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**ROBUST SUMMARIES and  
SIDS DOSSIER for:  
2-Ethylhexanoic Acid**

.....

**CAS No. 149-57-5**

Sponsor Country: U.S.A.

DATE: Revised July 2001

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## SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH-C-OH} \\    \\  \text{CH}_2\text{-CH}_3  \end{array}  $
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

## SIDS SUMMARY

CAS-Number 149-57-5							
	Info. Available	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degradability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5							
	Info Available	OECD Summary	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for  
Available Data on HPV Chemicals

**1.0    General Information**

**Name of Sponsor Country:** United States of America

**Contact Point:**

Mr. Charles Auer  
Director - Existing Chemicals Assessment Division  
Office of Toxic Substances (TS-788)  
U S Environmental Protection Agency  
401 M Street, SW  
Washington, DC 20460  
Telephone (202) 382-3442  
Fax (202) 382-7883, -7884, -7885

**Name of Lead Organization:** US Environmental Protection Agency

**2.0    Chemical Identity**

\*    2.1    **CAS Number:** 149-57-5

\*    2.2    **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

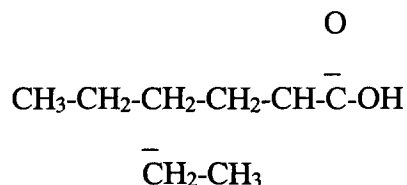
**2.3    Common Synonyms:**

$\alpha$ -Ethylcaproic acid  
2-Ethylcaproic acid  
 $\alpha$ -Ethylhexanoic acid  
Butylethylacetic acid  
Ethylhexoic acid  
2-EHA  
2-EH acid  
2-Ethylhexoic acid  
2-Ethylhexanoic acid  
2-Butylbutanoic acid  
2-Heptanecarboxylic acid  
3-Heptanecarboxylic acid  
Octanoic acid

2.4 **Empirical Formula:**



\* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **Physical-Chemical Data**

\* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

**Method** (e.g., OECD, others): None provided.

**GLP:** YES [ ]  
NO [X]

**Comments:** Study predates GLP regulations.

**Reference:** Material Safety Data Sheet, Eastman Kodak Company.

\* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

**Method:** (e.g., OECD, Others): None provided.

**GLP:** YES [ ]  
NO [X]

**Comments:** Study predates GLP regulations.

**Reference:** Material Safety Data Sheet, Eastman Kodak Company.

\* 3.3 **Vapor Pressure:**

1.33 x 10<sup>-3</sup> kPa at 20°C

**Method** (e.g., OECD, others): None provided.

**GLP:** YES ☐  
NO ☒

**Comments:** Study predates GLP regulations.

**Reference:** Material Safety Data Sheet, Eastman Kodak Company.

\* 3.4 (A.) **Partition Coefficient n-Octanol/Water (Preferred Study)**

log Pow = 3 at 25°C

**Method:** calculated ☒  
measured ☐

**GLP:** YES ☐  
NO ☒

**Analytical Method:** Estimated by the method of Hansch and Leo

**Comments** (e.g., is the compound surface active or dissociative?):

**Reference:** Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

**Method:** calculated ☒  
measured ☐

**GLP:** YES ☐  
NO ☒

**Analytical Method:** Estimated by the method of Hansch and Leo

**Comments** (e.g., is the compound surface active or dissociative?):

**Reference:** Pamona College Medicinal Chemistry Project, Claremont, CA

\* 3.5 **Water Solubility:**

25 mg/L at 25°C

**Method** (e.g., OECD, others): None provided.

**GLP:** YES ☐  
NO ☒

**Analytical Method:** None provided.

**Comments:** Study predates GLP regulations.

**Reference:** Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup ☐ open cup ☒

**Method:**

**GLP:** YES ☐  
NO ☒

**Comments:** Study predates GLP regulations.

**Reference:** Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

**Method** (e.g., OECD, others): None provided.

**GLP:** YES ☐  
NO ☒

**Test Results:** Autoignition temperature = 371°C

Cool flame autoignition = 199°C

**Comments:** Study predates GLP regulations.

**Reference:** Material Safety Data Sheet, Eastman Kodak Company.

### 3.8 pH in Water

pH at mg/L (Water)

pKa = 4.8 at 25°C

**Method** (e.g., OECD, others): Not provided.

**GLP:** YES [ ]  
NO [X]

**Comments:** Data predates GLP regulations.

**Reference:** Product literature, Union Carbide Corp. (1974).

### 3.9 Other Data

**Density:** 0.90 cc at 20°C

**Comments:** Study predates GLP regulations.

**Reference:** Material Safety Data Sheet, Eastman Kodak Company.

## 4.0 Source of Exposure

- \* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
- 4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.  
  
**Reference:** Roderick D. Gerwe, Ph.D., Eastman Chemical Company
- \* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.
- 4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

#### 4.5 Other Remarks:

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

**Reference:** Roderick D. Gerwe, Ph.D., Eastman Chemical Company

#### 5.0 **Environmental Fate and Pathways**

##### \* 5.1 **Degradability (Biotic and Abiotic)**

###### 5.1.1 **Biodegradability**

**Test Substance:** 2-Ethylhexanoic acid

**Test Type:** aerobic [X], anaerobic [ ]

**Test Medium:** Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

**Test Method:** According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, I. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

**GLP:** YES [ ]  
NO [X]

**Test Results:** BOD<sub>5</sub> = 60 % of Theoretical (2.44 g O<sub>2</sub>/g test substance).  
BOD<sub>10</sub> = 76 % of Theoretical (2.44 g O<sub>2</sub>/g test substance).  
BOD<sub>20</sub> = 83 % of Theoretical (2.44 g O<sub>2</sub>/g test substance).

**Comments:** Study predates GLP regulations.

**Reference:** G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

#### 5.1.2 Sewage Treatment

**Comments:** No Data Available.

#### 5.1.3 Stability in Air (e.g., photodegradability)

**Test Substance:**

**Test Method or Estimation Method** (e.g., OECD, others): Calculation

**GLP:** YES [ ]  
NO [ X]

**Test Results:** 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

**Reference:** Staples, 2000.

#### 5.1.4 Stability in Water (e.g., hydrolysis):

**Test Substance:**

**Test Method:** Calculation

**GLP:** YES [ ]  
NO [ X]

**Test Results:** See Staples report.

**Reference:** Staples, 2000.

#### 5.1.5 Identification of Main Mode of Degradability in Actual Use

No Data Available.

## 5.2 **Bioaccumulation**

**Test Substance:**

**Test Method** (e.g., OECD, others): Calculated

**GLP:** YES [ ]  
NO [ X]

**Test Results:** see Staples report

**Bioaccumulation Factor:**

**Calculated Results:**

**Comments:**

**Reference:** Staples, 2000.

## \* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

**Type of Transport and Distribution Processes between Compartments** (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

**Estimation of Environmental Concentrations:**

**Reference:** Staples, 2000.

## 5.4 **Monitoring Data (Environment):**

No Data Available.

## 6.0 **Ecotoxicological Data**

### \* 6.1 **Toxicity to Fish**

#### 6.1.1 **Results of Acute Tests**

**Test Substance:** 2-Ethylhexanoic acid

**Test Species:** Pimephales promelas (fathead minnow)

**Test Method:** Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static ☒, semi-static ☐, flow-through ☐  
Other (e.g., field observation) ☐

**GLP:** YES ☐  
NO ☒

**Test Results:**  $LC_{50} = 70$  mg/L after 96 hours at a pH of 5.3-5.5

**Comments:** Study predates GLP regulations. Test solutions were not buffered.

**Reference:** Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

#### 6.1.2 Results of Long-Term Tests e.g., prolonged toxicity, early life stage

**Test Substance:**

**Test Species:**

**Test Method** (e.g., OECD, others):

**GLP:** YES ☐  
NO ☐

**Test Results:** No Data Available.

**Comments:**

**Reference:**

\* 6.2 Toxicity to Daphnids

6.2.1 Results of Acute Tests

**Test Substance:** 2-Ethylhexanoic acid

**Test Species:** *Daphnia magna* (waterflea)

**Test Method** (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

**Test Concentration:** 31.25, 62.5, 125, 250, & 500 mg/L.

**Test Duration:** 48 hours.

**GLP:** YES [ ]  
NO [X]

**Test Results:** 48 hr EC<sub>50</sub> = 85.38 mg/L (slightly toxic),  
CI 95% = 79.77-91.38 mg/L  
48 hr EC<sub>0</sub> = 62.5 mg/L, 48 hr EC<sub>100</sub> = 125 mg/L

**Comments:** No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC<sub>0</sub> - highest tested concentration without effect after 48 hours. EC<sub>100</sub> - lowest tested concentration with 100% effect after 48 hours).

**Reference:** BASF Aktiengesellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 Results of Long-Term Tests e.g., Reproduction

**Test Substance:**

**Test Species:**

**Test Method** (e.g., OECD, others):

**GLP:** YES [ ]  
NO [ ]

**Test Results:** No Data Available.

**Comments:**

**Reference:**

\* 6.3 **Toxicity to Algae**

**Test Substance:** 2-Ethylhexanoic acid

**Test Species:** Scenedismus subspicatus

**Test Method** (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

**Test Concentration:** 0, 25, 50, 100, 250, or 500 mg/L.

**Test Duration:** 96 hours.

**GLP:** YES [ ]  
NO [X ]

**Test Results:**

72 hr EbC <sub>10</sub>	= 32.543 mg/L
72 hr EbC <sub>50</sub>	= 60.511 mg/L
96 hr EbC <sub>10</sub>	= 24.496 mg/L
96 hr EbC <sub>50</sub>	= 40.616 mg/L
72 hr EuC <sub>10</sub>	= 31.940 mg/L
72 hr EuC <sub>50</sub>	= 49.279 mg/L
96 hr EuC <sub>10</sub>	= 27.938 mg/L
96 hr EuC <sub>50</sub>	= 44.390 mg/L

**Comments:** Nominal concentrations tested. No analytical available on test concentrations.

**Reference:** BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

**Test Substance:**

**Test Species:**

**Test Method:**

**GLP:** YES [ ]  
NO [ ]

**Test Results:** No Data Available.

**Comments:**

**Reference:**

**6.5 Toxicity to Bacteria**

**Test Substance:**

**Test Species:**

**Test Method** (e.g., OECD, others):

**GLP:** YES ☐

NO ☐

**Test Results:** No Data Available.

**Comments:**

**Reference:**

\* **6.6 Toxicity to Terrestrial Organisms**

**6.6.1 Toxicity to Soil Dwelling Organisms**

**Test Results:** No Data Available.

**6.6.2 Toxicity to Plants**

**Test Results:** No Data Available.

**6.6.3 Toxicity to Birds**

**Test Results:** No Data Available.

**6.7 Biological Effects Monitoring (Including Biomagnification)**

**Test Results:** No Data Available.

**6.8 Biotransformation and Kinetics in Environmental Species**

No Data Available.

**7.0 Toxicological Data** (oral, dermal and inhalation, as appropriate)

\* **7.1 Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

**Test Substance:** 2-Ethylhexanoic acid

**Test Species/Strain:** Male Wistar Rats

**Test Method:** Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

**GLP:** YES ☐  
NO ☒

**Test Results:** Discriminating dose (for fixed dose only): LD<sub>50</sub> = 3000 g/kg

**Comments:** Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

**Reference:** Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, I. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity (Additional Study)**

**Test Substance:** 2-Ethylhexanoic acid

**Test Species/Strain:** Rats/strain not specified

**Test Method:** Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

**GLP:** YES ☐  
NO ☒

**Test Results:** Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD<sub>50</sub> or other measure of acute toxicity (e.g. in case of fixed-dose test):  
1600-3200 mg/kg

**Comments:** Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

**Reference:** Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

**Test Substance:** 2-Ethylhexanoic acid (99.6%) in corn oil

**Test Species/Strain:** Female Sprague-Dawley Rats

**Test Method:** Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

**GLP:** YES ☒  
NO ☐

**Test Results:** Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test):  
1600-3200 mg/kg

**Comments:**

**Reference:** Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

**Test Substance:** 2-Ethylhexanoic acid

**Test Species/Strain:** Rat/strain not specified

**Test Method:** Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

**GLP:** YES ☐  
NO ☒

**Test Results:** No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

**Comments:** Study predates GLP regulations. Body weight data not provided.

**Reference:** Fassett, D.W. (1955). Toxicity Report (Unpublished report).  
Laboratory of Industrial Medicine, Eastman Kodak Company.

### 7.1.3 Acute Dermal Toxicity

(A.) **Test Substance:** 2-Ethylhexanoic acid

**Test Species/Strain:** Guinea pig/strain not specified

**Test Method:** Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

**GLP:** YES ☐  
NO ☒

**Test Results:** LD50: 6.5 ml/kg

**Comments:** Study predates GLP regulations. No clinical observations cited. Body weights not measured.

**Reference:** Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, *J. Ind. Hyg. Toxicol.* 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

**Test Substance:** 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

**Test Species/Strain:** Guinea pig/strain not specified

**Test Method:** Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

**GLP:** YES ☐  
NO ☒

**Test Results:** Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

**Comments:** Study predates GLP regulations. Body weight data not provided.

**Reference:** Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

## 7.2 Corrosiveness/Irritation

### 7.2.1 Skin Irritation

(A.) **Test Substance:** 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

**Test Species/Strain:** Guinea pig/strain not specified

**Test Method:** Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

**GLP:** YES [ ]  
NO [X]

**Test Results:** Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

**Comments:** Study predates GLP regulations.

**Reference:** Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation (Preferred Study)**

**Test Substance:** 2-Ethylhexanoic acid

**Test Species/Strain:** New Zealand White Rabbit

**Test Method:** US Department of Transportation Corrosivity Test

**GLP:** YES ☒  
NO ☐

**Test Results:** The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

**Comments:**

**Reference:** Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

### 7.2.2 Eye Irritation

**Test Substance:** 2-Ethylhexanoic acid

**Test Species/Strain:** Rabbit/strain not designated

**Test Method** (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

**GLP:** YES ☐  
NO ☒

**Test Results:** Severe corneal irritation was observed

**Comments:** Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

**Reference:** Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, I. Ind. Hyg. Toxicol. 26, 269-273.

### 7.3 Skin Sensitisation

**Test Substance:**

**Test Method:**

**GLP:** YES ☐  
NO ☐

**Test Results:** No Data Available.

**Comments:**

**Reference:**

\* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

**Test Species/Strain:** Male Fischer 344 Rats

**Test Method:** Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

**GLP:** YES ☐  
NO ☒

**Test Results:** Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

**Comments:** No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

**Reference:** Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

**Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

**Test Species/Strain:** Male Fischer 344 Rats

**Test Method:** Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

**GLP:** YES ☐  
NO ☒

**Test Results:** Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

**Comments:** Study predates GLP regulations.

**Reference:** Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. *Toxicol. Lett.* 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

**Test Substance:** 2-Ethylhexanoic acid (>99.8%) in corn oil

**Test Species/Strain:** B6C3F1 Mice

**Test method:** Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

**GLP:** YES ☒  
NO ☐

**Test Results:** One animal from the mid-dose group was found dead and one control animal was euthanatized in *extremis*. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

**Comments:**

**Reference:** Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

**Test Substance:** 2-Ethylhexanoic acid (>99.8%) in corn oil

**Test Species/Strain:** Fischer-344 Rats

**Test Method:** Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each

animal was weighed, and the liver and kidneys examined microscopically.

**GLP:** YES ☒

NO ☐

**Test Results:** Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized *in extremis*. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

**Comments:**

**Reference:** Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

**Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

**Test Species/Strain:** B6C3F1 Mice

**Test Method:** Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

**GLP:** YES ☒

NO ☐

**Test Results:** Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-dose groups, respectively. One male from the mid-dose group was found dead

during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

**Comments:** 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

**Reference:** Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

**Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

**Test Species/Strain:** Fischer-344 Rats

**Test Method:** Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

**GLP:** YES ☒  
NO ☐

**Test Results:** Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and mid-dose groups. Absolute and relative (to body weight) liver weight were

significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

**Comments:** 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

**Reference:** Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

**Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

**Test Species/Strain:** B6C3F1 Mice

**Test Method:** USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

**GLP:** YES ☒  
NO ☐

**Test Results:** Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid-, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte

hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

**Comments:** 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

**Reference:** Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity (Preferred Study)**

**Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

**Test Species/Strain:** Fischer 344 Rats

**Test Method:** USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

**GLP:** YES ☒  
NO ☐

**Test Results:** Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid-, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights

occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

**Comments:** 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

**Reference:** Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

\* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

**Test Species/Strain:** *S. typhimurium* TA98 and TA100, with and without S-9

**Test Method:** Incubation with test substance for 2 days at 37°C in standard Ames test.

**GLP:** YES ☐  
NO ☒

**Test Results:** Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

**Comments:** No control values provided.

**Reference:** Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

**Test Substance:** 2-Ethylhexanoic acid in DMSO

**Test Species/Strain:** Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

**Test Method:** Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

**GLP:** YES ☐  
NO ☒

**Test Results:** Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate  
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

**Comments:** Conducted as part of Government contract. Not under GLP regulations.

**Reference:** Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

**Test Substance:**

**Test Method** (e.g., OECD, others):

**GLP:** YES ☐  
NO ☐

**Test Results:** No Data Available.

**Comments:**

**Reference:**

#### 7.5.3 Non-Bacterial Test *In Vivo*

**Test Substance:** 2-Ethylhexanol in corn oil (see comments)

**Test Species/Strain:** Mouse/B6C3F1

**Test Method** (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

**GLP:** YES [X]  
NO [ ]

**Test Results:** There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

**Comments:** The data from 2-ethylhexanol is directly applicable to the assessment of this endpoint for 2-ethylhexanoic acid due to the extensive metabolism of the former to the latter in vivo. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

**Reference:** Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). ( See also EPA OTS508477)

#### 7.6 Carcinogenicity

**Test Substance:**

**Test Species/Strain:**

**Test Method** (e.g., OECD, others):

GLP: YES [ ]  
NO [ ]

**Test Results:** No Data Available.

**Comments:**

**Reference:**

\* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

**Test Substance:** Sodium 2-Ethylhexanoate (99.5%) in drinking water

**Test Species/Strain:** Wistar rats

**Test Method** (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]  
NO [X]

**Test Results:** The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size

in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

**Comments:** Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

**Reference:** Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and

Postnatal Development in Wistar Rats. *Fundam. Appl. Toxicol.* in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

**Test Substance:** 2-Ethylhexanoic acid (neat)

**Test Species/Strain:** Wistar Rats

**Test Method** (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

**GLP:** YES ☐  
NO ☒

**Test Results:** The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

**Comments:** Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

**Reference:** Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethylhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. *Teratol.* 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity (Additional Study)**

**Test Substance:** Sodium 2-Ethylhexanoate (99%) in physiological saline

**Test Species/Strain:** Han:NMRI Mice

**Test Method** (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

**GLP:** YES ☐  
NO ☒

**Test Results:** A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryoletality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryoletality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

**Comments:** Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

**Reference:** Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. *Life Sci.* 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity (Additional Study)**

**Test Substance:** Sodium 2-Ethylhexanoate (99%) in drinking water

**Test Species/Strain:** Wistar rats

**Test Method** (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

**GLP:** YES ☐  
NO ☒

**Test Results:** The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs

was significantly higher in the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

**Comments:** There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

**Reference:** Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. *Fundam. Appl. Toxicol.* 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

**Test Substance:** Sodium 2-Ethylhexanoate (99%) in physiological saline

**Test Species/Strain:** SWV and C57BL/6NCrlBR Mice

**Test Method** (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour period; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

**GLP:** YES ☐  
NO ☒

**Test Results:** Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage

of resorptions increased at higher dose levels, and was also high in the animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

**Comments:** Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or

clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

**Reference:** Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. *Toxicol. Appl. Pharmacol.* 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

**Test Substance:** 2-Ethylhexanoic acid in corn oil

**Test Species/Strain:** Fischer 344 Rats

**Test Method** (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

**GLP:** YES ☒  
NO ☐

**Test Results:** No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae,

bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

**Comments:**

**Reference:** Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbancic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. *Fundam. Appl. Toxicol.* 20:199-209.

- (F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

**Test Substance:** 2-Ethylhexanoic acid in corn oil

**Test Species/Strain:** New Zealand White Rabbits

**Test Method** (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

**GLP:** YES ☒  
NO ☐

**Test Results:** One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of

animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

**Comments:**

**Reference:** Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbancic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. *Fundam. Appl. Toxicol.* 20:199-209.

**(G.) Teratogenicity/Developmental toxicity (Additional Study)**

**Test Substance:** 2-Ethylhexanoic acid in corn oil

**Test Species/Strain:** Female Sprague-Dawley Rats

**Test Method** (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into

three groups and fed diets as described for the second experiment. The animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg) was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]  
NO [X]

**Test Results:** The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

**Comments:** The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

**Reference:** Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. *Teratology* 53(2):p88, Abstract 21.

#### 7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

#### 7.9 Toxicodynamics, Toxicokinetics

**Test Substance:** [2-<sup>14</sup>C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmol) in corn oil

**Test Species/Strain:** Female Fischer 344 Rats

**Test Method:** Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]  
NO [ ]

**Test Results:** Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of  $0.19 \pm 0.11$  hrs,  $6.6 \pm 3.9$  hrs, and  $117 \pm 47$  hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration ( $0.32 \pm 0.04$  hrs,  $6.8 \pm 3.5$  hrs, and  $98.2 \pm 32.8$  hrs). Dermal application resulted in slower absorption with peak blood levels occurring  $5.7 \pm 0.4$  hours after application and a half-life of  $3.2 \pm 0.1$  hr. Elimination was biphasic with half-lives of  $4.2 \pm 0.2$  and  $251 \pm 135$  hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

<u>Route</u>	<u>Dose</u>	<u>Percentage Excreted as</u>
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid

Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

**Comments:**

**Reference:** English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

**8.0 Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

**8.1 Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m<sup>3</sup> (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the

work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to  $0.7 \text{ mg/m}^3$ ;  $0.0007 \text{ mg/L}$ ), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be  $2.33 \times 10^{-4} \text{ mg/kilogram body weight/8 hour workday}$ . The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

**Reference:** Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. *Int. Arch. Occup. Environ. Health*, 62:213-216.

9.0 **Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets**

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 **Availability and Reference(s) for Existing Review(s)**

## APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (\*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(\*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(\*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

# 1. General Information

ID 27253-31-2

Date November 7, 2005

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**201-16121B1**

## 1.0 SUBSTANCE INFORMATION

Generic Name :  
Chemical Name : Neodecanoic acid, cobalt salt  
CAS Registry No. : 27253-31-2  
Component CAS Nos. :  
EINECS No. : 248-373-0  
Structural Formula :  $\text{Co}(\text{C}_{10}\text{H}_{19}\text{O}_2)_2$   
Molecular Weight : 401.46  
Synonyms and : Cobalt neodecanoate  
Tradenames :  
References :

## 2. Physico-Chemical Data

ID 27253-31-2

Date November 7, 2005

### 2.1 MELTING POINT

**Type** : Melting Point/Melting Range Determination  
**Guideline/method** : OECD No. 102; EPA OPPTS 830.7200  
**Value** : -27°C to -26°C (freezing point)  
**Decomposition** : at °C  
**Sublimation** :  
**Year** : 2003  
**GLP** : Yes  
**Test substance** : Cobalt neodecanoate, Code 105 (Lot No. 48278), 14.16% cobalt, thick blue/purple liquid  
**Method** : OECD No. 102, Melting Point/Melting Range, July 1995; EPA Product Properties Test Guidelines, OPPTS 730.7200, Melting Point/Melting Range, March 1998.  
**Method detail** : A combination of the thermal analysis (calorimeter) and visual test (capillary method) was used. The test material (3 mL) was cooled down slowly in a glass tube immersed in a cooling bath, while the consistency of the sample was judged visually. Temperature in the sample was measured concurrently with a thermocouple. The test was carried out in duplicate. The freezing point is defined as the temperature at which phase transition from liquid to solid occurs, and ideally corresponds to the melting point.  
**Result** : No heat effect was observed from which the freezing point could be deduced. The freezing point was therefore determined visually. The test material was a viscous liquid at room temperature and was a frozen (solid) at -26 to -27°C.  
**Remark** : **Supporting data for dissociation products:**  
**Acid:** The reported melting point for neodecanoic acid is -39°C (Appendix D).  
**Metal:** The reported melting point for cobalt chloride is 735°C (Appendix G).  
**Reliability** : [1] Reliable without restriction  
**Reference** : Tognucci, A., 2003. Determination of the Melting Point/Melting Range of Cobalt neodecanoate, RCC Study No. 849099, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

### 2.2 BOILING POINT

**Type** :  
**Guideline/method** :  
**Value** : 426 - 517 °C  
**Decomposition** :  
**Year** :  
**GLP** :  
**Test substance** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** : **Supporting data for dissociation products:**  
**Acid:**  
The reported boiling point for neodecanoic acid is 243 - 253°C (Appendix D).  
**Metal:** The reported boiling point for cobalt chloride is 1,049°C (Appendix G).  
**Reliability** :  
**Reference** : Material Safety Data Sheet for 14% Cobalt Neodecanoate, OMG Americas, Inc.

## 2. Physico-Chemical Data

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### 2.3 DENSITY

Type : Specific gravity  
Guideline/method :  
Value : 1.07 at 25°C  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** The reported density for neodecanoic acid is 0.91 g/cm<sup>3</sup> at 20°C (Appendix D).  
**Metal:** The reported density for cobalt chloride is 3.367 at 25°C (Appendix G).  
  
Reliability :  
Reference : Material Safety Data Sheet for 14% Cobalt Neodecanoate, OMG Americas, Inc.

### 2.4 VAPOR PRESSURE

Type :  
Guideline/method :  
Value : hPa at °C  
Decomposition :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** The reported vapor pressure for neodecanoic acid is approx. 0.29 hPa at 50°C (Appendix D).  
  
Reliability :  
Reference :

### 2.5 PARTITION COEFFICIENT

Type :  
Guideline/method :  
Partition coefficient :  
Log Pow :  
pH value :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** The calculated Log Kow for neodecanoic acid is 3.90 (Appendix D).  
**Metal:** Not applicable. Cobalt chloride dissociates in water.  
  
Reliability :  
Reference :

## 2. Physico-Chemical Data

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### 2.6.1 SOLUBILITY IN WATER

Type	:	Water solubility determination
Guideline/method	:	OECD 105; EPA OPPTS 830.7840
Value	:	309.5 mg/L at 20°C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	
Description	:	
Stable	:	
Deg. product	:	
Year	:	2004
GLP	:	Yes
Test substance	:	Cobalt neodecanoate, Code 105 (Lot No. 48278), 14.16% cobalt
Deg. products CAS#	:	
Method	:	OECD 105, Water Solubility, 1995; EPA Product Properties Test Guidelines, OPPTS 830.7840, Water Solubility; Column Elution Method, Shake Flask Method, 1998.
Method detail	:	A preliminary test indicated that the column elution method was appropriate. Glass beads (6.06 g) were weighed and placed in a 25 mL round bottom flask. Test item (0.20 g) was added and dissolved in dichloromethane (6 mL). The dichloromethane was then evaporated using a gentle stream of nitrogen. The loaded carrier was poured into the elution column which was then filled with water. The system was equilibrated for approximately 2 hours. Elution of the test material from the carrier was performed using a circulation pump. Test temperature was 20°C. The flow rate was 0.52 mL/min in the first part of the test (about 98 hours) and 0.26 mL/min in the second part of the test (about 23 hours). The apparatus was run until equilibration of the saturation column was obtained, defined by at least five successive samples whose concentrations do not differ more than 30%. The column eluate was sampled at intervals of at least 1 hour to determine the concentration of cobalt, using atomic absorption spectroscopy.
Result	:	Based upon the results of 12 samples, the cobalt solubility was 43.8 mg/L (S.D. $\pm$ 1.3 mg/L), which corresponds to a water solubility of cobalt neodecanoate of 309.5 mg/L.
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> The calculated water solubility for neodecanoic acid is 68.97 mg/L at 25°C (Appendix D). <b>Metal:</b> The reported water solubility for cobalt chloride is 450 g/L at 7°C (Appendix G).
Reliability	:	[1] Reliable without restriction
Reference	:	Tognucci, A., 2004. Determination of the water solubility of cobalt neodecanoate. RCC Study No. 849101, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

### 2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	230 °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	

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**Result**  
**Remark**

:

: **Supporting data for dissociation products:**

**Acid:** The reported flash point for neodecanoic acid is approx. 122°C (Appendix D).

**Metal:** not applicable

**Reliability**  
**Reference**

:

: Material Safety Data Sheet for 14% Cobalt Neodecanoate, OMG Americas, Inc.

### 3. Environmental Fate & Transport

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#### 3.1.1 PHOTODEGRADATION

Type  
Guideline/method :  
Light source :  
Light spectrum :  
Relative intensity : based on  
Spectrum of substance : lambda (max, >295nm) :  
epsilon (max) :  
epsilon (295) :  
Conc. of substance : at °C  
**DIRECT PHOTOLYSIS**  
Half-life (t<sub>1/2</sub>) :  
Degradation : % after  
Quantum yield :  
**INDIRECT PHOTOLYSIS**  
Sensitizer :  
Conc. of sensitizer :  
Rate constant :  
Degradation :  
Deg. product :  
Year :  
GLP :  
Test substance :  
Deg. products CAS# :  
Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** Neodecanoic acid is calculated to have a half-life of 17 hours when subject to indirect photolysis (hydroxyl radicals). (Appendix D).  
**Metal:** Photodegradation not applicable for cobalt chloride.  
Reliability :  
Reference :

#### 3.1.2 DISSOCIATION

Type : Dissociation constant determination  
Guideline/method : OECD 112  
pKa : 6.52 at 20°C  
Year : 2002  
GLP : Yes  
Test substance : Cobalt neodecanoate, 14%, received from OMG. Purple semi-solid, purity of 14.2% cobalt.  
Approximate water solubility : 2.9 mg/L as determined by Inductively Coupled Plasma Atomic Emission Spectrometry in preliminary study  
Method : OECD Guideline 112, Dissociation Constants in Water  
Method detail : Three replicate samples of neodecanoic acid, cobalt salt were prepared at a nominal concentration of 1.5 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 1.0 mg/mL stock solution of the test substance in tetrahydrofuran. Each sample was titrated against 0.0025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.  
Result : Mean (N = 3) pKa value was 6.52 (SD = 0.00351) at 20°C

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**Remark** : The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).  
**Reliability** : [1] Reliable without restriction.  
**Reference** : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of neodecanoic acid, cobalt salts, Wildlife International, Ltd. Study No. 534C-119, conducted for the Metals Carboxylate Coalition.

#### 3.2.1 MONITORING DATA

**Type of measurement** :  
**Media** :  
**Concentration** :  
**Substance measured** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** :  
**Reliability** :  
**Reference** :

#### 3.3.1 TRANSPORT (FUGACITY)

**Type** :  
**Media** :  
**Air** : % (Fugacity Model Level I)  
**Water** : % (Fugacity Model Level I)  
**Soil** : % (Fugacity Model Level I)  
**Biota** : % (Fugacity Model Level II/III)  
**Soil** : % (Fugacity Model Level II/III)  
**Year** :  
**Test substance** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** : **Supporting data for dissociation products:**  
**Acid:** Fugacity Model, Level III calculations for neodecanoic acid predict 3.55% in air, 37% in water, 57.5% in soil, and 1.96% in sediment when emitted in equal amounts to air, water and soil (Appendix D).  
**Reliability** :  
**Reference** :

#### 3.5 BIODEGRADATION

**Type** :  
**Guideline/method** :  
**Inoculum** :  
**Concentration** : related to  
related to  
**Contact time** :  
**Degradation** : (±) % after day(s)  
**Result** :  
**Kinetic of test subst.** : % (specify time and % degradation)  
%  
%  
%

### 3. Environmental Fate & Transport

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Control substance	:	%
Kinetic	:	%
	:	%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> Neodecanoic acid is not readily biodegradable, with 11% degradation after 28 days using the manometric respirometry test (Appendix D). <b>Metal:</b> Metal does not degrade.
Reliability	:	
Reference	:	

#### 3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

## 4. Ecotoxicity

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### 4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> For neodecanoic acid, the 96-h LC50 for the rainbow trout ( <i>Oncorhynchus mykiss</i> ) was reported as 37.2 mg/L. Other reported LC50 values range from 32 – 181 mg/L (Appendix D). <b>Metal:</b> For cobalt chloride, the 96-h LC50 was 1.41 mg Co/L for the highly sensitive rainbow trout, <i>Onchorynchus mykiss</i> . Other fish species are less sensitive with 96-h LC50 values ranging from 22.0 to 333 mg Co/L (Appendix G).
Reliability	:	
Reference	:	

### 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> For neodecanoic acid, the 48-h LL50 for <i>Daphnia magna</i> has been reported as 47.1 mg/L. For the copepod, <i>Acartia tonsa</i> , the 96-h LC50 for neodecanoic acid has been reported as 25 mg/L. (Appendix D).

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**Metal:** For cobalt chloride, the 48-h EC50 values for *Daphnia magna* have been reported as 1.52 mg Co/L and as 5.5 mg Co/L. For *Ceriodaphnia dubia*, 48-h LC50 values ranged from 2.35 to 4.60 mg Co/L (Appendix G).

Reliability :  
Reference :

### 4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :  
Guideline/method :  
Species :  
Endpoint :  
Exposure period :  
NOEC :  
LOEC :  
EC0 :  
EC10 :  
EC50 :  
Other :  
Other :  
Other :  
Limit test :  
Analytical monitoring :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Metal:** For cobalt chloride, the 96-h EC50 for *Chorella vulgaris* was 0.52 mg Co/L. For the duckweed *Lemna minor*, the 7-d IC50 was 16.9 mg Co/L, while for the blue-green alga *Spirulina platensis* the 96-h EC50 was 23.8 mg Co/L (Appendix G).

Reliability :  
Reference :

## 5. Toxicity

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### 5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo :  
Type :  
Guideline/method :  
Species :  
Number of animals :  
Males :  
Females :  
Doses :  
Males :  
Females :  
Vehicle :  
Route of administration :  
Exposure time :  
Product type guidance :  
Decision on results on :  
acute tox. tests :  
Adverse effects on :  
prolonged exposure :  
Half-lives : 1<sup>st</sup>.  
2<sup>nd</sup>.  
3<sup>rd</sup>.

Toxic behavior :  
Deg. product :  
Deg. products CAS# :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

#### Supporting data for dissociation products:

**Acid:** Neodecanoic acid is relatively resistant to biotransformation and does not readily form bioactive metabolites (Appendix D). Thus it would be primarily eliminated in the urine as glucuronic acid conjugates or by deakylation (Katz, G.V., and D. Guest, 1994. "Aliphatic Carboxylic Acids," in Patty's Industrial Hygiene and Toxicology, 4<sup>th</sup> ed., Vol. 2, Part E. Clayton, G.D., and F.E. Clayton, eds., John Wiley and Sons).

**Metal:** Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal, with increasing solubility resulting in increasing absorption. Approximately 13-34% of cobalt chloride, a soluble form, is absorbed in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine. Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (Appendix G).

Reliability :  
Reference :

#### 5.1.1 ACUTE ORAL TOXICITY

Type :  
Guideline/Method :

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Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> The acute oral LD50 of neodecanoic acid in the rat has been reported as 2000 mg/kg or as 2700 – 3450 mg/kg (Appendix D). <b>Metal:</b> For cobalt chloride hexahydrate, the oral LD50 in rats was 766 mg/kg (equivalent to 190 mg Co/kg). Other reported LD50s range from 19.8 to 85.5 mg Co/mg bw in rats. In mice, the LD50 for cobalt chloride was reported as 89.3 mg Co/kg bw (Appendix G).
Reliability	:	
Reference	:	

### 5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> The acute inhalation LC50 for neodecanoic acid in the rat has been reported as >511 mg/m <sup>3</sup> for an exposure period of 6 hours. Other reported data include LC50 values > 3.0 mg/L for rats and mice, and LC50 values of > 73 ppm for rats, mice and guinea pigs. The acute inhalation LC50 for neodecanoic acid chloride in the rat has been reported as approximately 0.40 mg/L for an exposure period of 4 hours. (Appendix D). <b>Metal:</b> No acute inhalation toxicity studies were located for cobaltous chloride (Appendix G).
Reliability	:	
Reference	:	

### 5.1.3 ACUTE DERMAL TOXICITY

Type	:
Guideline/method	:

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Species :  
Strain :  
Sex :  
Number of animals :  
Vehicle :  
Doses :  
LD50 :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** The acute dermal LD50 for neodecanoic acid in the rabbit has been reported as >3160 mg/kg. For rats this value was >3640 mg/kg. (Appendix D).

**Metal:** Increased proliferation of lymphatic cells was seen in rats, mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (Appendix G).

Reliability :  
Reference :

### 5.2.1 SKIN IRRITATION

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :  
Concentration :  
Exposure :  
Exposure time :  
Number of animals :  
Vehicle :  
Classification :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** Neodecanoic acid was found to be non-irritating to skin when tested on the rabbit (Appendix D).

**Metal:** Dermatitis is a common result of dermal exposure to cobalt in humans and is probably caused by an allergic reaction (Appendix G).

Reliability :  
Reference :

### 5.2.2 EYE IRRITATION

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :

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Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> Neodecanoic acid was found to cause eye irritation when tested on the rabbit using the Draize test. (Appendix D).
Reliability	:	
Reference	:	

### 5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> When administered to rats in their feed for 3 months, the NOAEL for a 30% preparation of neodecanoic acid was 500 ppm. The LOAEL was 1500 ppm and included changes in the renal tubules of both male and female rats. Morphological changes in the thyroid, including hyperplasia, were also seen in male rats at the feeding level of 1500 ppm. Albino rabbits receiving 10 dermal applications of neodecanoic acid over a 14 day period showed no systemic effects, resulting in a NOAEL of 2.26 g/kg. Beagle dogs receiving oral capsules containing neodecanoic acid daily for a period of 13 weeks did not show adverse effects at dosing levels of approximately 30 mg/kg and below. Effects on body weight and declines in hematocrit, hemoglobin and erythrocyte values were seen at doses of 94.8 mg/kg and above. (Appendix D). <b>Metal:</b> Repeated oral dosing of rats with cobalt chloride hexahydrate for 8 weeks indicated the NOAEL was 0.6 mg Co/kg and the LOAEL was 2.5 mg Co/kg, based upon changes in hemoglobin content and numbers of

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erythrocytes. Another study reported oral doses of 0.5 and 2.5 mg Co/kg for 7 months stimulated hematopoiesis and decreased immunological reactivity in rats, while doses of 0.05 mg Co/kg had no effects. (Appendix G).

Reliability :  
Reference :

### 5.5 GENETIC TOXICITY 'IN VITRO'

Type :  
Guideline/method :  
System of testing :  
Species :  
Strain :  
Test concentrations :  
Cytotoxic concentr. :  
Metabolic activation :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

#### Supporting data for dissociation products:

**Acid:** Neodecanoic acid produced negative results in the Ames *Salmonella* assay (OECD Method 471) against four strains of bacteria when tested without metabolic activation at levels up to 1500 µg/plate and without activation at levels up to 1000 µg/plate. Neodecanoic acid produced negative results in a cytogenetic assay (OECD Method 473) with cultured human lymphocytes when tested both with and without metabolic activation at levels up to 800 µg/ml. (Appendix D).

**Metal:** Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt chloride, are generally non-mutagenic in bacterial assays, including plate incorporation and fluctuation assays with *Salmonella typhimurium* TA strains and *Escherichia coli* WP2. However, a weak positive mutagenic response has been found in the rec assay with *Bacillus subtilis* and in Chinese hamster V9 cells. DNA damage in isolated human lymphocytes was observed at 6.0 mg Co/L in the alkaline comet assay, and an increase in sister chromatid exchanges has been observed in human lymphocytes and macrophages (Appendix G).

Reliability :  
Reference :

### 5.6 GENETIC TOXICITY 'IN VIVO'

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :  
Route of admin. :  
Exposure period :  
Doses :  
Year :  
GLP :  
Test substance :  
Method :

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Method detail :

Result :

Remark :

**Supporting data for dissociation products:**

**Metal:** Oral administration of cobalt chloride hexahydrate to mice (20 – 80 mg.kg bw) produced a concentration-dependent increase in chromosomal aberrations. A dose-dependent increase in the incidence of micronucleated polychromatic erythrocytes was observed in mice subsequent to i.p. injection of  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ , at doses of 25 – 90 mg Co/kg bw. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL). (Appendix G).

Reliability :

Reference :

### 5.8.2 DEVELOPMENTAL TOXICITY

Type :

Guideline/method :

Species :

Strain :

Sex :

Route of admin. :

Exposure period :

Frequency of treatment :

Duration of test :

Doses :

Control group :

NOAEL maternal tox. :

NOAEL teratogen. :

Other :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark :

**Supporting data for dissociation products:**

**Acid:** In a 3-generation study with Sprague-Dawley rats, F1 and F2 generation pups born to parents fed up to 1500 ppm neodecanoic acid did not show any effects upon body weight, appearance, or behavior. There were no findings of treatment-related toxicity, abnormalities, or pathology. (Appendix D).

**Metal:** In a developmental toxicity study with cobalt chloride exposure (5.4 to 21.8 mg Co/kg/day) in rats from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects were observed on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (Appendix G).

Reliability :

Reference :

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### 5.8.3 TOXICITY TO REPRODUCTION

Type :  
Guideline/method :  
In vitro/in vivo :  
Species :  
Strain :  
Sex :  
Route of admin. :  
Exposure period :  
Frequency of treatment :  
Duration of test :  
Doses :  
Control group :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** In an oral (feeding) multi-generation rat reproduction study with neodecanoic acid, no adverse effects were observed in the parental generation or the F<sub>1</sub> and F<sub>2</sub> generations at feeding levels up to 1500 ppm in the diet. (Appendix D).

**Metal:** Cobalt exposure (as cobalt chloride hexahydrate in drinking water for 12 -13 weeks) affected male reproductive parameters for mice in a time- and dose-dependent manner. All dose levels (23.0 – 72.1 mg Co/kg-day) caused decreases in testicular weight and epididymal sperm concentration. Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (Appendix G).

Reliability :  
Reference :

### 6.0 OTHER INFORMATION

#### 6.1 CARCINOGENICITY

**Supporting data for dissociation products:**

**Metal:** The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals. "No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt." (ATSDR Sept 2001 Draft; see Appendix G).

#### 6.2 Skin Sensitization

**Supporting data for dissociation products:**

**Acid:** Neodecanoic acid was not found to be sensitizing when tested on the guinea pig using the Magnusson and Kligman maximization test. (Appendix D).

201-16121B2

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# I U C L I D

## D a t a s e t

Existing Chemical	Substance ID: 26896-20-8
CAS No.	26896-20-8
EINECS Name	neodecanoic acid
EINECS No.	248-093-9
Molecular Weight	173
Molecular Formula	C10H20O2

Dataset created by: EUROPEAN COMMISSION - European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

Creation date: 18-FEB-2000

Number of Pages: 26

Chapters: all

Edition: Year 2000 CD-ROM edition

Flags: non-confidential

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European Chemicals Bureau

**1.0.1 OECD and Company Information**

**Name:** BASF AG  
**Street:** Karl-Bosch-Str  
**Town:** 67056 Ludwigshafen  
**Country:** Germany

**Name:** Deutsche Exxon Chemical G.m.b.H  
**Street:** Neusser Landstrasse, 16  
**Town:** 5000 Koeln  
**Country:** Germany  
**Phone:** 0221.7703.1  
**Telefax:** 0021.7703.355  
**Telex:** 8885260

**Name:** Exxon Chemical France  
**Street:** 31 Place des Corolles  
**Town:** F-92098 PARIS La Defense 2  
**Country:** France  
**Phone:** (331) 49 03 50 00  
**Telefax:** 47 73 55 11  
**Telex:** 611191 F  
**Cedex:** 31

**Name:** EXXON CHEMICAL HOLLAND BV  
**Street:** Botlekweg 121  
**Town:** 3197 KA Botlek Rt.  
**Country:** Netherlands  
**Phone:** 31.1819.55971  
**Telefax:** 31.1819.55983

**Name:** Shell Nederland Chemie B.V.  
**Street:** Vondelingenweg 601  
**Town:** 3196 KK Rotterdam  
**Country:** Netherlands

**1.0.2 Location of Production Site**

-

**1.0.3 Identity of Recipients**

-

**1.1 General Substance Information**

**Substance type:** organic  
**Physical status:** liquid

**Substance type:** organic  
**Physical status:**

1. General Information

date: 18-FEB-2000  
Substance ID: 26896-20-8

**1.1.1 Spectra**

-

**1.2 Synonyms**

2,2-dimethyloctanoic acid

**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

Neo Acids C10

**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

Neo decanoic acid prime

**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

Neodecanoic acid (8CI, 9CI)

**Source:** BASF AG Ludwigshafen

Topper 5E

**Source:** BASF AG Ludwigshafen

Wiltz 65

**Source:** BASF AG Ludwigshafen

**1.3 Impurities**

-

**1.4 Additives**

-

**1.5 Quantity**

**Quantity** 50 000 - 100 000 tonnes

**1.6.1 Labelling**

-

**1.6.2 Classification**

-

**1.7 Use Pattern**

**Type:** type  
**Category:** Non dispersive use

1. General Information

date: 18-FEB-2000  
Substance ID: 26896-20-8

**Type:** type  
**Category:** Use in closed system

**Type:** industrial  
**Category:** Chemical industry: used in synthesis

**Type:** use  
**Category:** Intermediates

**1.7.1 Technology Production/Use**

-

**1.8 Occupational Exposure Limit Values**

**Type of limit:** other: Exxon Internal Occupational Exposure Limit  
**Limit value:** 25 mg/m3  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(1)

**Type of limit:**  
**Limit value:**  
**Remark:** None established  
**Source:** Shell Nederland Chemie B.V. Rotterdam

**1.9 Source of Exposure**

-

**1.10.1 Recommendations/Precautionary Measures**

-

**1.10.2 Emergency Measures**

-

**1.11 Packaging**

-

**1.12 Possib. of Rendering Subst. Harmless**

-

**1.13 Statements Concerning Waste**

-

**1.14.1 Water Pollution**

-

**1.14.2 Major Accident Hazards**

-

**1.14.3 Air Pollution**

-

**1.15 Additional Remarks**

**Remark:**

DIPOSAL OPTIONS

Dispose to licensed disposal contractor.  
Recover or recycle if possible; otherwise incinerate in  
licensed waste incineration plant.

TRANSPORT INFORMATION

Not dangerous for conveyance under UN, IMO, ADR/RID and  
IATA/ICAO codes.

**Source:**

Shell Nederland Chemie B.V. Rotterdam

**1.16 Last Literature Search**

-

**1.17 Reviews**

-

**1.18 Listings e.g. Chemical Inventories**

-

### 2.1 Melting Point

**Value:** ca. -39 degree C  
**Decomposition:** no  
**Method:** other: ASTM D97  
**GLP:** no  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

### 2.2 Boiling Point

**Value:** ca. 243 - 253 degree C at 1013.25 hPa  
**Decomposition:** no  
**Method:** Directive 84/449/EEC, A.2 "Boiling point/boiling range"  
**GLP:** no data  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(2)

**Value:** ca. 243 - 253 degree C at 1013.25 hPa  
**Decomposition:** no  
**Method:** Directive 84/449/EEC, A.2 "Boiling point/boiling range"  
**GLP:** no data  
**Source:** Exxon Chemical France PARIS La Defense 2

(3)

### 2.3 Density

**Type:** density  
**Value:** ca. .91 g/cm3 at 20 degree C  
**Method:** other: ASTM D4052  
**GLP:** no data  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(2)

**Type:** density  
**Value:** ca. .91 g/cm3 at 20 degree C  
**Method:** other: ASTM D4052  
**GLP:** no data  
**Source:** Exxon Chemical France PARIS La Defense 2

(3)

#### 2.3.1 Granulometry

-

**2.4 Vapour Pressure**

**Value:** ca. .29 hPa at 50 degree C  
**Method:** other (calculated): not specified  
**GLP:** no data  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(2)

**Value:** ca. .29 hPa at 50 degree C  
**Method:** other (calculated): not specified  
**GLP:** no data  
**Source:** Exxon Chemical France PARIS La Defense 2

(3)

**2.5 Partition Coefficient**

**log Pow:** ca. 3.6  
**Method:** other (calculated)  
**Year:**  
**GLP:** no data  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

**2.6.1 Water Solubility**

**Value:** < .1 vol% at 25 degree C  
**Qualitative:** not soluble  
**Method:** other: not specified  
**GLP:** no data  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(2)

**Value:** < .1 vol% at 25 degree C  
**Qualitative:** not soluble  
**Method:** other: not specified  
**GLP:** no data  
**Source:** Exxon Chemical France PARIS La Defense 2

(3)

**2.6.2 Surface Tension**

-

**2.7 Flash Point**

**Value:** ca. 122 degree C  
**Type:** open cup  
**Method:** other: ASTM D92  
**Year:**  
**GLP:** no data  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(2)

**Value:** ca. 122 degree C  
**Type:** open cup  
**Method:** other: ASTM D92  
**Year:**  
**GLP:** no data  
**Source:** Exxon Chemical France PARIS La Defense 2

(3)

**2.8 Auto Flammability**

-

**2.9 Flammability**

-

**2.10 Explosive Properties**

-

**2.11 Oxidizing Properties**

-

**2.12 Additional Remarks**

-

**3.1.1 Photodegradation**

-

**3.1.2 Stability in Water**

-

**3.1.3 Stability in Soil**

-

**3.2 Monitoring Data (Environment)**

-

**3.3.1 Transport between Environmental Compartments**

-

**3.3.2 Distribution**

-

**3.4 Mode of Degradation in Actual Use**

-

**3.5 Biodegradation**

Type:

Inoculum:

Method:

Year:

GLP:

Test substance:

Remark: ThOD = 2.6 g/g. COD = 0.3 g/l (estimated). BOD5 < 4% COD.

Source: EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(4)

**3.6 BOD5, COD or BOD5/COD Ratio**

-

**3.7 Bioaccumulation**

-

**3.8 Additional Remarks**

-

**AQUATIC ORGANISMS****4.1 Acute/Prolonged Toxicity to Fish**

**Type:** static  
**Species:** Carassius auratus (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**LC50:** = 2.6  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** other TS: 30% preparation of neodecanoic acid.  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(5)

**Type:** static  
**Species:** Carassius auratus (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**NOEC:** = 56  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(6)

**Type:** static  
**Species:** Cyprinodon variegatus (Fish, estuary, marine)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**LC0:** = 100  
**LC50:** = 181  
**LC100:** > 320  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(7)

## 4. Ecotoxicity

date: 18-FEB-2000  
Substance ID: 26896-20-8

**Type:** static  
**Species:** Lepomis macrochirus (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**LC50:** = 4.9  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** other TS: 30% preparation of neodecanoic acid.  
**Remark:** 48 hr static LC50 = 5.6 mg/l.  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(8)

**Type:** static  
**Species:** Lepomis macrochirus (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**LC50:** = 60  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** 24 hr static LC50 > 280 mg/l. 48 hr. static LC50 = 94 mg/l.  
72hr static LC50 = 77 mg/l.  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(9)

**Type:** static  
**Species:** Lepomis macrochirus (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**LC50:** = 60  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** 24 hr static LC50 > 280 mg/l. 48 hr. static LC50 = 94 mg/l.  
72hr static LC50 = 77 mg/l.  
**Source:** Exxon Chemical France PARIS La Defense 2

(10)

**Type:** static  
**Species:** Lepomis macrochirus (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**NOEC:** = 32  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(11)

**4.2 Acute Toxicity to Aquatic Invertebrates**

**Species:** Daphnia magna (Crustacea)  
**Exposure period:** 48 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**NOEC:** < 13  
**EC50:** = 47.11  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(12)

**Species:** Daphnia magna (Crustacea)  
**Exposure period:** 48 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**NOEC:** < 13  
**EC50:** = 47.11  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** Exxon Chemical France PARIS La Defense 2

(13)

**Species:** other: Acartia tonsa (copepod)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**LC50 :** = 25  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** 24 hr. LC50 > 100 mg/l. 48 hr LC50 = 65 mg/l. 72 hr. LC50  
= 43 mg/l.  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(14)

**Species:** other: Acartia tonsa (copepod)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** no data  
**LC50 :** = 25  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** 24 hr. LC50 > 100 mg/l. 48 hr LC50 = 65 mg/l. 72 hr. LC50  
= 43 mg/l.  
**Source:** Exxon Chemical France PARIS La Defense 2

(14)

**4.3 Toxicity to Aquatic Plants e.g. Algae**

-

**4.4 Toxicity to Microorganisms e.g. Bacteria**

-

**4.5 Chronic Toxicity to Aquatic Organisms****4.5.1 Chronic Toxicity to Fish**  
-**4.5.2 Chronic Toxicity to Aquatic Invertebrates**  
-**TERRESTRIAL ORGANISMS****4.6.1 Toxicity to Soil Dwelling Organisms**  
-**4.6.2 Toxicity to Terrestrial Plants**  
-**4.6.3 Toxicity to other Non-Mamm. Terrestrial Species**

**Species:** other avian: bobwhite quail  
**Endpoint:** mortality  
**Expos. period:**  
**Unit:** other: ppm  
**LC50:** > 5620  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

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**4.7 Biological Effects Monitoring**  
-**4.8 Biotransformation and Kinetics**  
-**4.9 Additional Remarks**  
-

**5.1 Acute Toxicity****5.1.1 Acute Oral Toxicity**

Type: LD50  
Species: rat  
Sex:  
Number of  
Animals:  
Vehicle:  
Value: 2700 - 3450 mg/kg bw  
Method: other: not specified  
Year: GLP: no data  
Test substance: as prescribed by 1.1 - 1.4  
Source: EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

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**5.1.2 Acute Inhalation Toxicity**

Type: LC50  
Species: rat  
Sex:  
Number of  
Animals:  
Vehicle:  
Exposure time: 6 hour(s)  
Value: > 73 ppm  
Method: other: not specified  
Year: GLP: no data  
Test substance: as prescribed by 1.1 - 1.4  
Source: EXXON CHEMICAL HOLLAND BV Botlek Rt..  
Deutsche Exxon Chemical G.m.b.H Koeln

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Type: LC50  
Species: rat  
Sex:  
Number of  
Animals:  
Vehicle:  
Exposure time: 6 hour(s)  
Value: > 73 ppm  
Method: other: not specified  
Year: GLP: no data  
Test substance: as prescribed by 1.1 - 1.4  
Source: Exxon Chemical France PARIS La Defense 2

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## 5. Toxicity

date: 18-FEB-2000  
Substance ID: 26896-20-8

Type: LC50  
Species: mouse  
Sex:  
Number of  
Animals:  
Vehicle:  
Exposure time: 6 hour(s)  
Value: > 73 ppm  
Method: other: not specified  
Year: GLP: no data  
Test substance: as prescribed by 1.1 - 1.4  
Source: EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(19)

Type: LC50  
Species: mouse  
Sex:  
Number of  
Animals:  
Vehicle:  
Exposure time: 6 hour(s)  
Value: > 73 ppm  
Method: other: not specified  
Year: GLP: no data  
Test substance: as prescribed by 1.1 - 1.4  
Source: Exxon Chemical France PARIS La Defense 2

(18)

Type: LC50  
Species: guinea pig  
Sex:  
Number of  
Animals:  
Vehicle:  
Exposure time: 6 hour(s)  
Value: > 73 ppm  
Method: other: not specified  
Year: GLP: no data  
Test substance: as prescribed by 1.1 - 1.4  
Source: EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(17)

Type: LC50  
Species: guinea pig  
Sex:  
Number of  
Animals:  
Vehicle:  
Exposure time: 6 hour(s)  
Value: > 73 ppm  
Method: other: not specified  
Year: GLP: no data  
Test substance: as prescribed by 1.1 - 1.4  
Source: Exxon Chemical France PARIS La Defense 2

(18)

**5.1.3 Acute Dermal Toxicity**

Type: LD50  
Species: rat  
Sex:  
Number of  
Animals:  
Vehicle:  
Value: > 3640 mg/kg bw  
Method: other  
Year: GLP: no  
Test substance: as prescribed by 1.1 - 1.4  
Source: EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(20)

Type: LD50  
Species: rat  
Sex:  
Number of  
Animals:  
Vehicle:  
Value: > 3640 mg/kg bw  
Method: other  
Year: GLP: no  
Test substance: as prescribed by 1.1 - 1.4  
Source: Exxon Chemical France PARIS La Defense 2

(21)

**5.1.4 Acute Toxicity, other Routes**

-

**5.2 Corrosiveness and Irritation****5.2.1 Skin Irritation**

Species: rabbit  
Concentration:  
Exposure:  
Exposure Time:  
Number of  
Animals:  
PDII:  
Result: not irritating  
EC classificat.: not irritating  
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"  
Year: GLP: yes  
Test substance: as prescribed by 1.1 - 1.4  
Source: EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

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**5.2.2 Eye Irritation**

**Species:** rabbit  
**Concentration:**  
**Dose:**  
**Exposure Time:**  
**Comment:**  
**Number of Animals:**  
**Result:** irritating  
**EC classificat.:** irritating  
**Method:** Draize Test  
**Year:** **GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

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**5.3 Sensitization**

**Type:** Guinea pig maximization test  
**Species:** guinea pig  
**Number of Animals:**  
**Vehicle:**  
**Result:** not sensitizing  
**Classification:** not sensitizing  
**Method:** other: Magnusson and Kligman maximisation test  
**Year:** **GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

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**5.4 Repeated Dose Toxicity**

**Species:** rat **Sex:** male/female  
**Strain:** other: albino  
**Route of admin.:** oral feed  
**Exposure period:** 3 months  
**Frequency of treatment:** daily  
**Post. obs. period:**  
**Doses:** 500, 1500, 5000 and 15000 ppm  
**Control Group:** yes  
**NOAEL:** = 500 ppm  
**LOAEL:** = 1500 ppm  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** other TS: 30% preparation of neodecanoic acid.  
**Remark:** The 15,000 ppm group showed a DECREASED BODY WEIGHT and a DECREASE IN HEMATOCRIT HEMOGLOBIN and RED BLOOD CELL COUNTS. There were MORPHOLOGICAL CHANGES IN THE THYROID, characterized by HYPERPLASIA of the follicular epithelium, manifested by increased cell height, increased cellularity, vacuolization of the follicular epithelium and irregularity of the follicular walls. These changes were seen at the high dose and as low as 1500 ppm in the male rats. The female rats showed this effect at 15,000 and 5000 ppm only. HEPATOTOXIC CHANGES were seen in the male and female rats at 15000 and 5000 ppm. There were RENAL CHANGES affecting the TUBULES of both the male and female rats at 15000, 5000 and 1500 ppm.  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

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**Species:** rat **Sex:** male/female  
**Strain:** other: albino  
**Route of admin.:** oral feed  
**Exposure period:** 3 months  
**Frequency of treatment:** daily  
**Post. obs. period:**  
**Doses:** 500, 1500, 5000 and 15000 ppm  
**Control Group:** yes  
**NOAEL:** = 500 ppm  
**LOAEL:** = 1500 ppm  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** other TS: 30% preparation of neodecanoic acid.  
**Remark:** The 15,000 ppm group showed a DECREASED BODY WEIGHT and a DECREASE IN HEMATOCRIT HEMOGLOBIN and RED BLOOD CELL COUNTS. There were MORPHOLOGICAL CHANGES IN THE THYROID, characterized by HYPERPLASIA of the follicular epithelium, manifested by increased cell height, increased cellularity, vacuolization of the follicular epithelium and irregularity of the follicular walls. These changes were seen at the high dose and as low as 1500 ppm in the male rats. The

## 5. Toxicity

date: 18-FEB-2000  
Substance ID: 26896-20-8

female rats showed this effect at 15,000 and 5000 ppm only.  
HEPATOTOXIC CHANGES were seen in the male and female rats  
at 15000 and 5000 ppm. There were RENAL CHANGES affecting  
the TUBULES of both the male and female rats at 15000, 5000  
and 1500 ppm.

**Source:** Exxon Chemical France PARIS La Defense 2

(24)

**Species:** rabbit **Sex:** male  
**Strain:** other: albino  
**Route of admin.:** dermal  
**Exposure period:** 14 days  
**Frequency of treatment:** 10 applications  
**Post. obs. period:**  
**Doses:** 0.5 and 2.5 ml/kg  
**Control Group:** yes  
**NOAEL:** > 2.5  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(25)

**Species:** rabbit **Sex:** male  
**Strain:** other: albino  
**Route of admin.:** dermal  
**Exposure period:** 14 days  
**Frequency of treatment:** 10 applications  
**Post. obs. period:**  
**Doses:** 0.5 and 2.5 ml/kg  
**Control Group:** yes  
**NOAEL:** > 2.5  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** Exxon Chemical France PARIS La Defense 2

(26)

## 5. Toxicity

date: 18-FEB-2000  
Substance ID: 26896-20-8

**Species:** dog **Sex:** male/female  
**Strain:** other: beagle  
**Route of admin.:** other: oral capsule  
**Exposure period:** 13 weeks  
**Frequency of treatment:** daily  
**Post. obs. period:**  
**Doses:** 9.48, 30, 94.8 or 300 mg/kg/day  
**Control Group:** yes  
**NOAEL:** ca. 30 mg/kg  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Frequent EMESIS and/or DIARRHEA was seen in the 94.8 and 300 mg/kg dose groups. WEIGHT SUPPRESSION was also seen at these doses. DECLINES IN HEMATOCRIT, HEMOGLOBIN and ERYTHROCYTE VALUES were seen at 94.8 and 300 mg/kg groups. No characteristic or consistent compound-related organ alterations were noted at terminal necropsy. Significant LIVER/BODY WEIGHT RATIO INCREASES were seen in the high dose group.  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H Koeln

(27)

**Species:** dog **Sex:** male/female  
**Strain:** other: beagle  
**Route of admin.:** other: oral capsule  
**Exposure period:** 13 weeks  
**Frequency of treatment:** daily  
**Post. obs. period:**  
**Doses:** 9.48, 30, 94.8 or 300 mg/kg/day  
**Control Group:** yes  
**NOAEL:** ca. 30 mg/kg  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Frequent EMESIS and/or DIARRHEA was seen in the 94.8 and 300 mg/kg dose groups. WEIGHT SUPPRESSION was also seen at these doses. DECLINES IN HEMATOCRIT, HEMOGLOBIN and ERYTHROCYTE VALUES were seen at 94.8 and 300 mg/kg groups. No characteristic or consistent compound-related organ alterations were noted at terminal necropsy. Significant LIVER/BODY WEIGHT RATIO INCREASES were seen in the high dose group.  
**Source:** Exxon Chemical France PARIS La Defense 2

(27)

**5.5 Genetic Toxicity 'in Vitro'**

**Type:** Ames test  
**System of testing:** TA 1535, TA 1537, TA 98, TA 100  
**Concentration:** 6.1 - 1500 ug/plate (-S9: 6.1 - 1000; +S9: 18.5 - 1500)  
**Metabolic activation:** with and without  
**Result:** negative  
**Method:** OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"  
**Year:** **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(28)

**Type:** Cytogenetic assay  
**System of testing:** cultured human lymphocytes  
**Concentration:** 100 - 800 ug/ml (-S9: 100 - 400; +S9: 250 - 800)  
**Metabolic activation:** with and without  
**Result:** negative  
**Method:** OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"  
**Year:** **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical France PARIS La Defense 2  
Deutsche Exxon Chemical G.m.b.H Koeln

(29)

**5.6 Genetic Toxicity 'in Vivo'**

-

**5.7 Carcinogenicity**

-

**5.8 Toxicity to Reproduction**

**Type:** other: modified 3 generation  
**Species:** rat **Sex:** male/female  
**Strain:** other: albino  
**Route of admin.:** oral feed  
**Exposure Period:** 3 generations  
**Frequency of treatment:** daily  
**Premating Exposure Period**  
**male:** 9 weeks  
**female:** 9 weeks  
**Duration of test:** 3 generations  
**Doses:** 100, 500 and 1500 ppm  
**Control Group:** yes  
**NOAEL Parental:** > 1500 ppm  
**NOAEL F1 Offspr.:** > 1500 ppm  
**NOAEL F2 Offspr.:** > 1500 ppm  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** There was no evidence at any test level of an adverse effect on the survival, appearance, behavior, body weight gain and food consumption on the parental generation; on the reproductive performance of the parents; or on the growth, appearance and behavior of the offspring. Gross and microscopic pathological findings revealed no evidence of a compound-related effect at any of the dietary levels.  
**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Deutsche Exxon Chemical G.m.b.H. Koeln

(30)

**Type:** other: modified 3 generation  
**Species:** rat **Sex:** male/female  
**Strain:** other: albino  
**Route of admin.:** oral feed  
**Exposure Period:** 3 generations  
**Frequency of treatment:** daily  
**Premating Exposure Period**  
**male:** 9 weeks  
**female:** 9 weeks  
**Duration of test:** 3 generations  
**Doses:** 100, 500 and 1500 ppm  
**Control Group:** yes  
**NOAEL Parental:** > 1500 ppm  
**NOAEL F1 Offspr.:** > 1500 ppm  
**NOAEL F2 Offspr.:** > 1500 ppm  
**Method:** other: not specified  
**Year:** **GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** There was no evidence at any test level of an adverse effect on the survival, appearance, behavior, body weight gain and food consumption on the parental generation; on the reproductive performance of the parents; or on the growth, appearance and behavior of the offspring. Gross and microscopic pathological findings revealed no evidence of a

**Source:** compound-related effect at any of the dietary levels.  
Exxon Chemical France PARIS La Defense 2

(30)

**5.9 Developmental Toxicity/Teratogenicity**

-

**5.10 Other Relevant Information**

-

**5.11 Experience with Human Exposure**

-

6. References

date: 18-FEB-2000  
Substance ID: 26896-20-8

- (1) Exxon Occupational Exposure Limits for Chemical Contaminants (1993-94).
- (2) Exxon Chemical International Material Safety Data Sheet for Neodecanoic acid.
- (3) Exxon Chemical International Material Safety Data Sheet for Neodecanoic acid.
- (4) Exxon Research and Engineering unpublished report 80MR 2017.
- (5) Woodard Research Corp. (1966). Safety evaluation of MRD-64-1 and MRD-66-1 in goldfish and bluegill sunfish. Sept. 9, 1966. Exxon unpublished report 66MRL 18.
- (6) Woodard Research Corp. (1966). Safety evaluation of MRD-64-3 and MRD-66-1 in goldfish and bluegill sunfish. Sept. 9, 1966. Exxon unpublished report 66MRL 18.
- (7) Toxicity of MRD-77-120 to sheepshead minnows (*Cyprinodon variegatus*). Performed by EG&G Bionomics for Exxon Corp. Exxon unpublished report 78MRR 237.
- (8) Woodard Research Corp. (1966). Safety evaluation of MRD-64-3 and MRD-66-1 in goldfish and bluegill sunfish. Sept. 9, 1966. Exxon unpublished report 66MRL 18.
- (9) Biodegradation and Ecotoxicity of oxo alkyl acetate. Exxon Corp Research and Environmental Health Division (unpublished report MR 6000.85).
- (10) Biodegradation and Ecotoxicity of oxo alkyl acetate. Exxon Corp Research and Environmental Health Division (unpublished report MR 6000.85).
- (11) Woodard Research Corp. (1966). Safety evaluation of MRD-64-3 and MRD-66-1 in goldfish and bluegill sunfish. Sept. 9, 1966. Exxon unpublished report 66MRL 18.
- (12) Acute toxicity of MRD-77-120 to the water flea (*Daphnia magna*). Performed by EG&G Bionomics for Exxon Corp. Exxon unpublished report 78MRR 215.
- (13) Acute toxicity of MRD-77-120 to the water flea (*Daphnia magna*). Performed by EG&G Bionomics for Exxon Corp. Exxon unpublished report 78MRR 215.
- (14) Acute toxicity of MRD-77-120 to the calanoid copepod (*Acartia tonsa*), a marine zooplankton. Performed by EG&G Bionomics for Exxon Corp. Exxon unpublished report 78MRR 266.

6. References

date: 18-FEB-2000  
Substance ID: 26896-20-8

- (15) Acute Oral LD50 - Bobwhite quail. Performed by Hazleton Laboratories for Esso Research and Engineering. Exxon unpublished report 66MRL 11.
- (16) Acute Oral Administration - Rats. Project number 145-254. Performed by Hazleton Laboratories for Esso Research and Engineering. May 26, 1966. Unpublished Exxon report.
- (17) Evaluation of the acute inhalation toxicity of MRD-82-117 in rats, mice and guinea pigs. Exxon unpublished report 82MRL 32.
- (18) Evaluation of the acute inhalation toxicity of MRD-82-117 in rats, mice and guinea pigs. Exxon unpublished report 82MRL 32.
- (19) Evaluation of the acute inhalation toxicity of MRD-82-117 in rats, mice and guinea pigs. Exxon unpublished report 82MRL 32.
- (20) Acute toxicity, skin and eye irritancy and skin sensitization potential of Versatic 10. Unpublished report, Shell Research TLGR.0024.77 (1977).
- (21) Acute toxicity, skin and eye irritancy and skin sensitization potential of Versatic 10. Unpublished report, Shell Research TLGR.0024.77 (1977).
- (22) Primary Dermal Irritation Study in the Rabbit. Performed by Exxon Biomedical Sciences for Exxon Chemical International. Project number 194704, test material MRD-91-947. Exxon unpublished report number 92MRL 43.
- (23) Acute toxicity, skin and eye irritancy and skin sensitisation potential of Versatic 10. Unpublished report, Shell Research TLGR.0024.77 (1977).
- (24) FINAL REPORT: Three Month Dietary Administration - Rats. Performed by Hazleton Laboratories for Esso Research and Engineering Co. July 1, 1966. Test material MRD-66-1.
- (25) Repeated Dermal Application - Rabbits. Test Material MRD-64-3. Test performed by Hazleton Laboratories for Esso Research and Engineering. July 17, 1964. Exxon unpublished report #64MRL 21.
- (26) Repeated Dermal Application - Rabbits. Test Material MRD-64-3. Test performed by Hazleton Laboratories for Esso Research and Engineering. July 17, 1964. Exxon unpublished report #64MRL 21.
- (27) Repeated dose toxicity study in beagle dogs. Performed by Hazleton Laboratories for Esso Research and Engineering. Exxon unpublished report #66MRL 12.

6. References

date: 18-FEB-2000  
Substance ID: 26896-20-8

- (28) Versatic 10: Bacterial Mutagenicity (Ames test).  
Unpublished Shell Report HSE.95.1078 (1995).
- (29) Versatic 10: Chromosome aberration in cultured human  
lymphocytes. Unpublished Shell Report HSE.95.1079 (1995).
- (30) Modified Three-Generation Reproduction Study - Rats.  
Performed by Hazleton Laboratories for Esso Research and  
Engineering. December 6, 1968. Test material MRD-67-21.  
Exxon unpublished report 68MRL 24.

**7.1 Risk Assessment**

-

# 1. General Information

ID 26896-20-8

Date November 7, 2005

201-10121B3

## 1.0 SUBSTANCE INFORMATION

Generic Name :  
Chemical Name : Neodecanoic acid  
CAS Registry No. : 26896-20-8  
Component CAS Nos. :  
EINECS No. : 248-093-9  
Molecular Formula :  $C_{10}H_{20}O_2$   
Molecular Weight : 172.27  
Synonyms and Tradenames : 2,2-dimethyloctanoic acid; Topper 5E; Wiltz 65  
References : IUCLID Dataset, February 2000 (Attached); TOXNET  
(<http://chem.sis.nlm.nih.gov>)

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## 2. Physico-Chemical Data

ID 26896-20-8

Date November 7, 2005

### 2.1 MELTING POINT

Type :  
Guideline/method : ASTM D97  
Value : -39°C  
Decomposition : at °C  
Sublimation :  
Year :  
GLP : No data  
Test substance : Neodecanoic acid  
Method :  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference : IUCLID dataset, 2000 (Attached)

### 2.2 BOILING POINT

Type :  
Guideline/method : Directive 84/449/EEC, A.2 "Boiling point/boiling range"  
Value : Approx. 243 - 253°C  
Decomposition :  
Year :  
GLP : No data  
Test substance : Neodecanoic acid  
Method :  
Method detail :  
Result :  
Remark : Calculated value of 262.37°C (adapted Stein and Brown method), MPBWIN v1.41 (EPIWIN v3.11)  
Reliability : [1] Reliable without restriction; reported experimental result and calculated result in agreement  
Reference : IUCLID dataset, 2000 (Attached)

### 2.3 DENSITY

Type :  
Guideline/method :  
Value : Approx. 0.91 g/cm<sup>3</sup> at 20°C  
Year :  
GLP : No data  
Test substance :  
Method : ASTM D4052  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference : IUCLID dataset, 2000 (Attached)

### 2.4 VAPOR PRESSURE

Type :  
Guideline/method :  
Value : Approx. 0.29 hPa at 50°C  
Decomposition :

## 2. Physico-Chemical Data

ID 26896-20-8

Date November 7, 2005

Year :  
GLP :  
Test substance : Neodecanoic acid  
Method : Calculated (not specified)  
Method detail :  
Result :  
Remark : Calculated value of 0.0071 mm Hg (modified Grain method), MPBWIN v1.41, EPIWIN v3.11  
Reliability :  
Reference : IUCLID dataset, 2000 (Attached)

### 2.5 PARTITION COEFFICIENT

Type :  
Guideline/method : WSKOW v1.41 (EPIWIN v3.11)  
Partition coefficient :  
Log Kow : 3.90  
pH value :  
Year :  
GLP :  
Test substance : Neodecanoic acid  
Method :  
Method detail :  
Result :  
Remark :  
Reliability : [1] Reliable without restriction; Calculated using scientifically acceptable method  
Reference :

### 2.6.1 SOLUBILITY IN WATER

Type :  
Guideline/method : WSKOW v1.41 (EPIWIN v3.11)  
Value : 68.97 mg/L at 25°C  
pH value :  
concentration : at °C  
Temperature effects :  
Examine different pol. :  
PKa : at °C  
Description :  
Stable :  
Deg. product :  
Year :  
GLP :  
Test substance :  
Deg. products CAS# :  
Method :  
Method detail :  
Result :  
Remark : Reported water solubility < 0.1% by volume at 25°C (IUCLID dataset, 2000; Attached)  
Reliability : [1] Reliable without restriction; Calculated using scientifically acceptable method  
Reference :

## 2. Physico-Chemical Data

ID 26896-20-8

Date November 7, 2005

### 2.7 FLASH POINT

Type	:	
Guideline/method	:	ASTM D92
Value	:	Approx. 122°C
Year	:	
GLP	:	No data
Test substance	:	
Method	:	Open cup
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	IUCLID dataset, 2000 (Attached).

### 3. Environmental Fate & Transport

ID 26896-20-8

Date November 7, 2005

#### 3.1.1 PHOTODEGRADATION

**Type**

Guideline/method : AOP v1.91 (EPIWIN v3.11)

Light source :

Light spectrum :

Relative intensity : based on

Spectrum of substance : lambda (max, &gt;295nm) :

epsilon (max) :

epsilon (295) :

Conc. of substance : at °C

**DIRECT PHOTOLYSIS**

Half-life (t1/2) :

Degradation : % after

Quantum yield :

**INDIRECT PHOTOLYSIS**

Sensitizer : OH

Conc. of sensitizer :

Rate constant : 7.5357 E-12 cm<sup>3</sup>/molecule-sec

Degradation : 50% after 17 hours

Deg. product :

Year :

GLP :

Test substance : Neodecanoic acid

Deg. products CAS# :

Method :

Method detail : Estimated melting point and boiling point used

Result : AOP Program (v1.91) Results:

=====

SMILES : O=C(O)CCCCC(C)(C)C

CHEM : Neodecanoic acid

MOL FOR: C10 H20 O2

MOL WT : 172.27

----- SUMMARY (AOP v1.91): HYDROXYL RADICALS -----

Hydrogen Abstraction = 7.0157 E-12 cm<sup>3</sup>/molecule-secReaction with N, S and -OH = 0.5200 E-12 cm<sup>3</sup>/molecule-secAddition to Triple Bonds = 0.0000 E-12 cm<sup>3</sup>/molecule-secAddition to Olefinic Bonds = 0.0000 E-12 cm<sup>3</sup>/molecule-secAddition to Aromatic Rings = 0.0000 E-12 cm<sup>3</sup>/molecule-secAddition to Fused Rings = 0.0000 E-12 cm<sup>3</sup>/molecule-secOVERALL OH Rate Constant = 7.5357 E-12 cm<sup>3</sup>/molecule-secHALF-LIFE = 1.419 Days (12-hr day; 1.5E6 OH/cm<sup>3</sup>)

HALF-LIFE = 17.033 Hrs

----- SUMMARY (AOP v1.91): OZONE REACTION -----

\*\*\*\*\* NO OZONE REACTION ESTIMATION \*\*\*\*\*

(ONLY Olefins and Acetylenes are Estimated)

**Remark****Reliability****Reference**

Experimental Database: NO Structure Matches  
Assumed data: 1.5E6 OH/cm<sup>3</sup>; 12-h day  
[1] Reliable without restriction; Calculated using scientifically acceptable method

### 3. Environmental Fate & Transport

ID 26896-20-8

Date November 7, 2005

#### 3.2.1 MONITORING DATA

Type of measurement :  
Media :  
Concentration :  
Substance measured :  
Method :  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference :

#### 3.3.1 TRANSPORT (FUGACITY)

Type :  
Media : Air-water-soil-sediment  
Year :  
Test substance : Neodecanoic acid  
Method : EPWIN v.3.11 - Calculation according to Mackay, Level III  
Method detail :  
Result : Level III Fugacity Model (Full-Output):

=====

Chem Name : Neodecanoic acid  
Molecular Wt: 172.27  
Henry's LC : 5.6e-006 atm-m3/mole (Henrywin program)  
Vapor Press : 0.00708 mm Hg (Mpbpwin program)  
Liquid VP : 0.0147 mm Hg (super-cooled)  
Melting Pt : 57.1 deg C (Mpbpwin program)  
Log Kow : 3.9 (Kowwin program)  
Soil Koc : 3.26e+003 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.55	34.1	1000
Water	37	360	1000
Soil	57.5	360	1000
Sediment	1.96	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	4.61e-011	662	325	22.1	10.8
Water	5.48e-011	652	339	21.7	11.3
Soil	1.21e-011	1.01e+003	0	33.7	0
Sediment	1.84e-011	8.64	0.359	0.288	0.012

Persistence Time: 305 hr  
Reaction Time: 392 hr  
Advection Time: 1.38e+003 hr  
Percent Reacted: 77.8  
Percent Advected: 22.2

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):  
Air: 34.06  
Water: 360  
Soil: 360  
Sediment: 1440

### 3. Environmental Fate & Transport

ID 26896-20-8

Date November 7, 2005

Biowin estimate: 2.971 (weeks)

**Advection Times (hr):**

Air: 100

Water: 1000

Sediment: 5e+004

-----

**Remark** :  
**Reliability** : [1] Reliable without restriction. Calculated using scientifically acceptable method  
**Reference** :

#### 3.5 BIODEGRADATION

**Type** : Manometric respirometry test  
**Guideline/method** : OECD 301F  
**Inoculum** : Domestic activated sludge  
**Concentration** : 31 – 50 mg/L related to

**Contact time** : 28 days  
**Degradation** : 11.0% (Mean) after 28 day(s)  
**Result** :  
**Kinetic of test subst.** : % (specify time and % degradation)  
%  
%  
%  
%

**Control substance** : Sodium benzoate, 44 mg/L  
**Kinetic** : %  
%

**Deg. product** :  
**Year** : 1996  
**GLP** : Yes  
**Test substance** : Neodecanoic acid  
**Deg. products CAS#** :  
**Method** :  
**Method detail** : As described in Appendix F, Part 3 (Robust summaries prepared by ExxonMobil Chemical Company)  
**Result** : The test substance is considered not readily biodegradable  
**Remark** :  
**Reliability** : [1] Reliable without restrictions (as assessed in Appendix F, Part 3)  
**Reference** : EG&G Bionomics, Wareham, MA. BW-78-1-005. As cited in Appendix F, Part 3.

#### 3.7 BIOCONCENTRATION

**Type** :  
**Guideline/method** :  
**Species** :  
**Exposure period** : at °C  
**Concentration** :  
**BCF** :  
**Elimination** :  
**Year** :

### 3. Environmental Fate & Transport

ID 26896-20-8

Date November 7, 2005

GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

## 4. Ecotoxicity

ID 26896-20-8

Date November 7, 2005

### 4.1 ACUTE TOXICITY TO FISH

Type	: Acute static renewal
Guideline/method	: OECD 203, Fish acute toxicity test
Species	: Rainbow trout ( <i>Oncorhynchus mykiss</i> )
Exposure period	: 96 hours
NOEC	:
LC0	:
LC50	: 37.2 mg/L (confidence interval 26.3 – 52.5 mg/L), based upon measured concentrations of mean of "old" and "new" samples
LC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	: Yes, using GC-FID
Year	: 1996
GLP	: Yes
Test substance	: Neodecanoic acid
Method	:
Method detail	: Individual Water Accomodated Fractions (WAFs) were prepared for each treatment, by mixing test substance for 24 hours. Tests were conducted in sealed aspirator bottles (no headspace). Other details described in Appendix F, Part 3. (Robust Summaries prepared by ExxonMobil Chemical Company)
Result	:
Remark	: Results (96-h LC50) for other species include: Bluegill ( <i>Lepomis macrochirus</i> ): 32 and 60 mg/L under static conditions; Goldfish ( <i>Carassius auratus</i> ): 56 mg/L under static conditions. Sheepshead minnow ( <i>Cyprinodon variegatus</i> ): 181 mg/L under static conditions. (See Attachment to Appendix D, IUCLID dataset, 2000)
Reliability	: [1] Reliable without restrictions (as assessed in Appendix F, Part 3)
Reference	: Exxon Biomedical Sciences, Inc. Fish Acute Toxicity Test, 118358. (As cited in Appendix F, Part 3, Robust Summaries prepared by ExxonMobil Chemical Company).

### 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	: Static acute
Guideline/method	: US EPA, Methods for acute toxicity with fish, macroinvertebrates and amphibians, EPA-660/3-75-009, 1975
Species	: <i>Daphnia magna</i>
Exposure period	: 48 hours
NOEC	:
EC0	:
EC50	: LL50 (lethal limit for 50%) = 47.1 mg/L (95% confidence interval 33.6 – 57.8 mg/L)
EC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	: No
Year	: 1977
GLP	: No
Test substance	: Neodecanoic acid
Method	:

## 4. Ecotoxicity

ID 26896-20-8

Date November 7, 2005

<b>Method detail</b>	:	Test substance was dissolved in triethylene glycol. Study design included control and solvent control. Details described in Appendix F, Part 3 (Robust summaries prepared by ExxonMobil Chemical Company)
<b>Result</b>	:	
<b>Remark</b>	:	The 48-h EC50 for <i>Daphnia magna</i> has been reported as 47.1 mg/L. For the copepod, <i>Acartia tonsa</i> , the 96-h LC50 has been reported as 25 mg/L. (See Attachment to Appendix D, IUCLID dataset, 2000)
<b>Reliability</b>	:	[2] Reliable with restrictions (as assessed in Appendix F, Part 3)
<b>Reference</b>	:	EG&G Bionomics, Wareham, MA. BW-78-1-005. (As cited in Appendix F, Part 3, Robust Summaries prepared by ExxonMobil Chemical Company)

### 4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

<b>Type</b>	:
<b>Guideline/method</b>	:
<b>Species</b>	:
<b>Endpoint</b>	:
<b>Exposure period</b>	:
<b>NOEC</b>	:
<b>LOEC</b>	:
<b>EC0</b>	:
<b>EC10</b>	:
<b>EC50</b>	:
<b>Other</b>	:
<b>Other</b>	:
<b>Other</b>	:
<b>Limit test</b>	:
<b>Analytical monitoring</b>	:
<b>Year</b>	:
<b>GLP</b>	:
<b>Test substance</b>	:
<b>Method</b>	:
<b>Method detail</b>	:
<b>Result</b>	:
<b>Remark</b>	:
<b>Reliability</b>	:
<b>Reference</b>	:

## 5. Toxicity

ID 26896-20-8

Date November 7, 2005

### 5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1 <sup>st</sup> . 2 <sup>nd</sup> . 3 <sup>rd</sup> .
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Neoacids C5-C28, including neodecanoic acid, are relatively resistant to biotransformation and do not readily form bioactive metabolites (Appendix F, Part 2; ExxonMobil Chemical Company, 2002). Thus it would be primarily eliminated in the urine as glucuronic acid conjugates or by deakylation (Katz and Guest, 1994).
Reliability	:	
Reference	:	

#### 5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute oral toxicity
Guideline/Method	:	
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	males
Number of animals	:	5 per dose
Vehicle	:	Corn oil for four lowest doses; two highest doses administered undiluted
Doses	:	34.6, 120, 417, 1450, 5000 and 10,000 mg/kg
LD50	:	2000 mg/kg (CL: 670 – 5980 mg/kg)
Year	:	1964
GLP	:	Pre-GLP
Test substance	:	Neodecanoic acid
Method	:	
Method detail	:	A single dose was given via gastric intubation. Animals were observed at 1,

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- Result** : 4 and 24 hours and once daily thereafter for 14 days, with subsequent necropsy. Other details described in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company)
- Remark** : There were no principal toxic effects or necropsy findings at the three lowest doses. All animals died at the three highest doses. At 5000 and 10,000 mg/kg, depression, dyspnea, ataxia and sprawling of the limbs were observed, as well as congestion of the lungs, liver, spleen, kidneys and adrenals. See Appendix F, Part 3 for detailed results
- Reliability** : The acute oral LD50 for the rat has been reported as 2700 – 3450 mg/kg bw (Attachment to Appendix D, IUCLID dataset, 2000)
- Reference** : [2] Reliable with restrictions (as assessed in Appendix F, Part 3)
- Esso Research and Engineering Company, 1964. Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report. As cited in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company).

### 5.1.2 ACUTE INHALATION TOXICITY

- Type** : Acute inhalation toxicity
- Guideline/method** :
- Species** : Rats, mice and Guinea pigs
- Strain** : Wistar rats, Swiss albino mice, and Harley Guinea pigs
- Sex** : Males and females
- Number of animals** : 10/sex/species
- Vehicle** : none
- Doses** : Liquid aerosol with a mean analytical concentration of 511 mg/m<sup>3</sup>
- Exposure time** : Single 6-hour exposure
- LC50** : > 511 mg/m<sup>3</sup>; mean particle size 2.99 ± 1.76 µm
- Year** : 1982
- GLP** : No
- Test substance** : Neodecanoic acid
- Method** :
- Method detail** : Groups of animals were exposed to either air only or to aerosolized test material. Exposure concentrations were determined on both a nominal and actual (gravimetric) basis. Animals were observed for mortality and toxic effects at 15 minute intervals during the first hour and hourly thereafter during exposure; and daily for signs of toxicity for 14 days post-exposure. Necropsy was performed on half the animals from each group on the first day post-exposure, with terminal necropsies on the remaining animals. Details are described in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company).
- Result** : No mortality occurred during the study. Animals exposed to the test material exhibited some signs of labored breathing, salivation and eye irritation during exposure. During the two-week post-exposure period, all guinea pigs appeared normal; however some mice appeared ungroomed and some rats exhibited anogenital staining and soft stool. At terminal sacrifice, exposed male mice exhibited a statistically significant decrease in the liver to body weight ratio; no other significant differences were observed.
- Remark** : The acute inhalation LC50 for rats and mice was reported as > 3.0 mg/L (Esso Research and Engineering Company, 1964; see Appendix F, Part 3). The acute inhalation LC50 for rats, mice, and guinea pigs in the rat has been reported as >73 ppm for an exposure period of 6 hours (Attachment to Appendix D, IUCLID dataset, 2000). The acute inhalation LC50 for neodecanoic acid chloride in the rat has been reported as approximately 0.40 mg/L for an exposure period of 4 hours (BASF Corp., 1993. Support: Letter from BASF Corp to USEPA re: results of the study on the acute inhalation toxicity LC50 of neodecanoic acid chloride as a vapor in rats w/cover letter dated 113093. Available in microfiche OTS0539604-1 from

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**Reliability** : the National Technical Information Service).  
**Reference** : [1] Reliable without restrictions (as assessed in Appendix F, Part 3)  
: Bio/dynamics, Inc., 1982. Evaluation of the acute inhalation toxicity in rats, mice, and guinea pigs. Unpublished report. As cited in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company).

### 5.1.3 ACUTE DERMAL TOXICITY

**Type** : Acute dermal toxicity  
**Guideline/method** :  
**Species** : Rabbits  
**Strain** : Albino  
**Sex** : Males and females  
**Number of animals** : 4 per dose  
**Vehicle** : none  
**Doses** : 50, 200, 794, 3160 mg/kg  
**LD50** : > 3160 mg/kg  
**Year** : 1964  
**GLP** : Pre-GLP  
**Test substance** : Neodecanoic acid  
**Method** :  
**Method detail** : A single dosing was conducted by applying undiluted test material to clipped, intact abdominal skin under a dental dam binder. After a 24-hour exposure period, animals were observed for mortality or toxic effects at 1, 4, and 24 hours and daily thereafter for 14 days, followed by necropsy. Details are described in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company).  
**Result** : No deaths, abnormal appearance, behavior, or weight gain or signs of pathology were observed. No dermal irritation was observed at the low dose; minimal irritation was seen at 200 mg/kg. At the 794 and 3160 mg/kg levels, a dose-dependent increase in the degree of irritation was observed, consisting of slight to moderate erythema and slight to moderate atonia and desquamation, subsiding over the course of the study. Additional details are described in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company).  
**Remark** : The acute dermal LD50 for neodecanoic acid in the rat has been reported as >3640 mg/kg (Attachment to Appendix D, IUCLID dataset, 2000).  
**Reliability** : [2] Reliable with restrictions (as assessed in Appendix F, Part 3)  
**Reference** : Esso Research and Engineering Company, 1964. Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report. As cited in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company).

### 5.2.1 SKIN IRRITATION

**Type** :  
**Guideline/method** : OECD 404, Acute Dermal Irritation/Corrosion  
**Species** : Rabbit  
**Strain** :  
**Sex** :  
**Concentration** :  
**Exposure** :  
**Exposure time** :  
**Number of animals** :  
**Vehicle** :  
**Classification** : Not irritating  
**Year** :  
**GLP** : Yes

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Test substance : Neodecanoic acid  
Method :  
Method detail :  
Result :  
Remark :  
Reliability : [4] Not assignable (secondary reference)  
Reference : Attachment to Appendix D, IUCLID dataset, 2000

### 5.2.2 EYE IRRITATION

Type :  
Guideline/method : Draize test  
Species : Rabbit  
Strain :  
Sex :  
Concentration :  
Dose :  
Exposure time :  
Number of animals :  
Vehicle :  
Classification :  
Year :  
GLP : No  
Test substance :  
Method :  
Method detail :  
Result : Irritating  
Remark :  
Reliability : [4] Not assignable (secondary reference)  
Reference : Attachment to Appendix D, IUCLID dataset 2000

### 5.4 REPEATED DOSE TOXICITY

Type :  
Guideline/method :  
Species : Rat  
Strain : Albino  
Sex : Males and females  
Number of animals :  
Route of admin. : Oral feed  
Exposure period : 3 months  
Frequency of treatment : Daily  
Post exposure period :  
Doses : 500, 1500, 5000 and 15,000 ppm  
Control group : Yes  
NOAEL : 500 ppm  
LOAEL : 1500 ppm  
Other :  
Year :  
GLP : No data  
Test substance : 30% preparation of neodecanoic acid  
Method :  
Method detail :  
Result : The LOAEL was 1500 ppm and included changes in the renal tubules of both male and female rats. Morphological changes in the thyroid, including hyperplasia, were also seen in male rats at the feeding level of 1500 ppm.  
Remark : Albino rabbits receiving 10 dermal applications of neodecanoic acid (0.4

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g/kg and 2.28 g/kg) over a 14 day period showed no systemic effects, resulting in a NOAEL of 2.26 g/kg (Appendix F, Part 3, Robust Summaries prepared by ExxonMobil Chemical Company). Beagle dogs receiving oral capsules containing neodecanoic acid daily for a period of 13 weeks did not show adverse effects at dosing levels of approximately 30 mg/kg and below. Effects on body weight and declines in hematocrit, hemoglobin and erythrocyte values were seen at doses of 94.8 mg/kg and above. (Attachment to Appendix D, IUCLID dataset, 2000).

**Reliability** : [4] Not assignable (secondary reference)  
**Reference** : Hazleton Laboratories, 1964. Final report: Three month dietary administration – Rats. Performed by Hazleton Laboratories for Esso Research and Engineering, July 17, 1964. Exxon unpublished report #64MRL 21. As cited in IUCLID dataset, 2000 (Attachment to Appendix D).

### 5.5 GENETIC TOXICITY 'IN VITRO'

**Type** : Ames test  
**Guideline/method** : OECD 471, "Genetic Toxicology: *Salmonella typhimurium* Reverse Mutation Assay"  
**System of testing** :  
**Species** : *Salmonella typhimurium*  
**Strain** : TA 1535, TA 1537, TA 98, TA 100  
**Test concentrations** : 6.1 – 1000 ug/plate without activation; 18.5 – 1500 ug/plate with activation  
**Cytotoxic concentr.** :  
**Metabolic activation** : With and without (S9)  
**Year** :  
**GLP** : yes  
**Test substance** : Neodecanoic acid  
**Method** :  
**Method detail** :  
**Result** : Negative  
**Remark** : Neodecanoic acid produced negative results in a cytogenetic assay (OECD Method 473; "Genetic toxicology: In-vitro mammalian cytogenetic test") with cultured human lymphocytes when tested both with and without metabolic activation at levels up to 800 µg/ml (Shell, 1995. Versatic 10: Chromosome aberration in cultured human lymphocytes, Unpublished Shell Report HSE.95.1079, as cited in IUCLID dataset, 2000, Attachment to Appendix D).

**Reliability** : [4] Not assignable (secondary reference)  
**Reference** : Shell, 1995. Versatic 10: Bacterial mutagenicity (Ames test). Unpublished Shell Report HSE 95.1078 (1995). As cited in IUCLID dataset, 2000 (Attachment to Appendix D).

### 5.6 GENETIC TOXICITY 'IN VIVO'

**Type** :  
**Guideline/method** :  
**Species** :  
**Strain** :  
**Sex** :  
**Route of admin.** :  
**Exposure period** :  
**Doses** :  
**Year** :  
**GLP** :  
**Test substance** :

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Method :  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference :

### 5.8.2 DEVELOPMENTAL TOXICITY

Type :  
Guideline/method :  
Species : Rat  
Strain : Sprague-Dawley  
Sex : Males and females  
Route of admin. : Dietary  
Exposure period :  
Frequency of treatment : Continuous  
Duration of test : 3 generations  
Doses : 0, 100, 500, 1500 ppm (5, 25, and 75 mg/kg/day)  
Control group : Purina Lab Chow, 0 ppm of test substance  
NOAEL maternal tox. : 1500 ppm  
NOAEL teratogen. : 1500 ppm  
Other :  
Other :  
Other :  
Year : 1968  
GLP : Pre-GLP  
Test substance : Neodecanoic acid  
Method :  
Method detail : A 3-generation study was performed, from which information on developmental toxicity can be obtained. Parental animals were maintained 9 weeks prior to a 3-week mating period. Weights of pups by sex were recorded at 24 hours and at weaning and all pups were observed for gross signs of abnormalities. Following the 21-day nursing period, representative pups from each litter were sacrificed and gross necropsies performed. The parents were re-mated to produce a second litter; selected pups were sacrificed and necropsied. Details described in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company)  
  
Result : F1 and F2 generation pups born to parents fed up to 1500 ppm neodecanoic acid did not show any effects upon body weight, appearance, or behavior. There were no findings of treatment-related toxicity, abnormalities, or pathology. (Appendix F, Part 3, Robust Summaries prepared by ExxonMobil Chemical Company)  
  
Remark :  
Reliability : [2] Reliable with restrictions (as assessed in Appendix F, Part 3).  
Reference : Hazleton Labs, Inc., 1968. Modified three-generation reproduction study – rats. Unpublished report. As cited in Robust Summaries prepared by ExxonMobil Chemical Company (Appendix F, Part 3).

### 5.8.3 TOXICITY TO REPRODUCTION

Type :  
Guideline/method :  
In vitro/in vivo :  
Species : Rat  
Strain : Sprague-Dawley  
Sex : Males and females  
Route of admin. : Dietary

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<b>Exposure period</b>	:	
<b>Frequency of treatment</b>	:	Continuous
<b>Duration of test</b>	:	3 generations
<b>Doses</b>	:	0, 100, 500, 1500 ppm in diet (0, 5, 25, and 75 mg/kg/day)
<b>Control group</b>	:	Purina lab chow, 0 ppm of test substance
<b>Year</b>	:	1968
<b>GLP</b>	:	Pre-GLP
<b>Test substance</b>	:	Neodecanoic acid
<b>Method</b>	:	
<b>Method detail</b>	:	Details described in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company)
<b>Result</b>	:	No adverse effects were observed in the parental generation or the F <sub>1</sub> and F <sub>2</sub> generations at feeding levels up to 1500 ppm in the diet. Details described in Appendix F, Part 3 (Robust Summaries prepared by ExxonMobil Chemical Company)
<b>Remark</b>	:	
<b>Reliability</b>	:	[2] Reliable with restrictions (as assessed in Appendix F, Part 3)
<b>Reference</b>	:	Hazleton Labs, Inc., 1968. Modified three-generation reproduction study – rats. Unpublished report. As cited in Robust Summaries prepared by ExxonMobil Chemical Company (Appendix F, Part 3).

### 6.0 OTHER INFORMATION

#### 6.1 Skin Sensitization

Neodecanoic acid was not found to be sensitizing when tested on the guinea pig using the Magnusson and Kligman maximization test. (Shell Research, 1997. Acute toxicity, skin and eye irritancy and skin sensitization potential of Versatic 10. Unpublished report, Shell Research TLGR.0024.77. As cited in Attachment to Appendix D, IUCLID dataset, 2000).

# 1. General Information

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201-16121B4

## 1.0 SUBSTANCE INFORMATION

Generic Name :  
Chemical Name : Fatty Acids, C9-C13 Neo, Cobalt Salts  
CAS Registry No. : 68955-83-9  
Component CAS Nos. :  
EINECS No. : 273-298-8  
Structural Formula :  $\text{Co}(\text{C}_9\text{H}_{17}\text{O}_2)_2$  ;  $\text{Co}(\text{C}_{13}\text{H}_{25}\text{O}_2)_2$   
Molecular Weight : 373.4 to 485.6  
Synonyms and Tradenames : Mixed (C9-C13) neoalkanoic acids, cobalt salts  
References : IUCLID Dataset, February 2000

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## 2. Physico-Chemical Data

ID 68955-83-9

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### 2.1 MELTING POINT

Type	: Melting Point/Melting Range Determination
Guideline/method	: OECD 103; EPA OPPTS 830.7200
Value	: Could not be determined
Decomposition	: at °C
Sublimation	:
Year	: 2003
GLP	: Yes
Test substance	: Fatty acids, C9-13-neo-cobalt salts, Lab Batch 1022-50 (LB1022-50), 16.05% cobalt, dark purple solid
Method	: OECD 102, Melting Point/Melting Range, July 1995; EPA Product Properties Test Guidelines, OPPTS 830.7200, Melting Point/Melting Range, March 1998
Method detail	: A differential scanning calorimeter (DSC 821, Fa, Mettler Toledo) was used to determine the melting point/range (the temperature or temperature range at which phase transition from solid to liquid state occurs). A preliminary test was conducted at a heating rate of 20 K/min from 25°C to 400°C and the quantities of heat absorbed or released were measured and recorded. The weight and appearance of the sample were recorded before and after the test. In the definitive test, the test material was heated at a rate of 5 K/min from 80°C to 250°C.
Result	: No endothermic heat effect was observed during definitive testing. It was concluded that the test substance does not melt under the conditions of the test.
Remark	: <b>Supporting data for dissociation products:</b> <b>Acid:</b> The melting point for fatty acids, C9-C13 neo, has been reported as less than -20°C (Appendix F, Part 1, IUCLID 2000 dataset). <b>Metal:</b> The reported melting point for cobalt chloride is 735°C (Appendix G).
Reliability	: [1] Reliable without restriction
Reference	: Tognucci, A., 2003. Determination of the Melting Point/Melting Range of Fatty acids, C9-13-neo-cobalt salts, RCC Study No. 849103, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland

### 2.2 BOILING POINT

Type	: Boiling Point/Boiling Range Determination
Guideline/method	: OECD 103; EPA OPPTS 830.7220
Value	: Could not be determined
Decomposition	:
Year	: 2003
GLP	: Yes
Test substance	: Fatty acids, C9-13-neo-cobalt salts, Lab Batch 1022-50 (LB1022-50), 16.05% cobalt, dark purple solid
Method	: OECD 103, Boiling Point, July 1995 (thermal analysis and visual with capillary tester); EPA Product Properties Test Guidelines, OPPTS 830.7220, Boiling Point/Boiling Range, August 1996
Method detail	: Thermal analysis was used for the preliminary test, while the visual test (capillary method) was used for the definitive test. In the preliminary test, the test substance was heated at a heating rate of 20 K/min from 25°C to 400°C and the quantities of heat absorbed or released were measured and recorded using a differential scanning calorimeter (DSC 821, Fa, Mettler Toledo). The weight and appearance of the sample were recorded before and after the test. In the definitive test (which was performed twice), the test substance was placed in two small glass tubes and boiling capillaries inserted. The samples were heated at a heating rate of 10 K/min from 25°C

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- Result** : to 400°C and observed visually through a lens for the appearance of a stream of bubbles.
- Remark** : In the thermal analysis, no relevant endothermic heat effect was observed from which the boiling point could be deduced. Using the capillary tester, the sample changed color to black at about 60°C and bubbles were observed at about 95°C. A boiling point or boiling range could not be determined under the conditions of the test.
- Reliability** : **Supporting data for dissociation products:**
- Reference** : **Acid:** The reported boiling point for fatty acids, C9-C13 neo, has been reported as approximately 195 - 280°C (Appendix F, Part 1, IUCLID 2000 dataset).  
**Metal:** The reported boiling point for cobalt chloride is 1,049°C (Appendix G).  
[1] Reliable without restriction  
Tognucci, A., 2003. Determination of the Boiling Point/Boiling Range of Fatty acids, C9-13-neo-cobalt salts, RCC Study No. 849104, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland

### 2.3 DENSITY

- Type** : Specific gravity
- Guideline/method** :
- Value** : 1.14 at 25°C
- Year** :
- GLP** :
- Test substance** :
- Method** :
- Method detail** :
- Result** :
- Remark** : **Supporting data for dissociation products:**  
**Acid:** The reported density for fatty acids, C9-C13, neo is 0.923 at 20°C (Appendix F, Part 1, IUCLID 2000 dataset).  
**Metal:** The reported density for cobalt chloride is 3.367 at 25°C (Appendix G).
- Reliability** :
- Reference** : Material Safety Data Sheet for Neo C9-C13 Acid, Cobalt Salts, OMG Americas, Inc.

### 2.4 VAPOR PRESSURE

- Type** :
- Guideline/method** :
- Value** : hPa at °C
- Decomposition** :
- Year** :
- GLP** :
- Test substance** :
- Method** :
- Method detail** :
- Result** :
- Remark** : **Supporting data for dissociation products:**  
**Acid:** The vapor pressure for fatty acids, C9-C13 neo, is reported 0.0065 hPa at 22.1°C (Directive 84/449/EEC A.4) (Appendix F, Part 1, IUCLID 2000 dataset).
- Reliability** :
- Reference** :

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### 2.5 PARTITION COEFFICIENT

Type :  
Guideline/method :  
Partition coefficient :  
Log Pow : at °C  
pH value :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** The log Kow for fatty acids, C9-C13 neo, was determined to be 3.05 – 3.17 following OECD Guideline 117 (Appendix F, Part 1, IUCLID 2000 dataset).  
**Metal:** Not applicable. Cobalt chloride dissociates in water.

Reliability :  
Reference :

### 2.6.1 SOLUBILITY IN WATER

Type : Water solubility determination  
Guideline/method : OECD 105; EPA OPPTS 830.7840  
Value : 28.3 mg/L at 20°C  
pH value :  
concentration : at °C  
Temperature effects :  
Examine different pol. :  
PKa : at °C  
Description :  
Stable :  
Deg. product :  
Year : 2004  
GLP : Yes  
Test substance : Fatty acids, C9-C13 neo-cobalt salts, Lab Batch 1022-50, 16.05% cobalt, dark purple solid

Deg. products CAS# :  
Method : OECD 105, Water Solubility, 1995; EPA Product Properties Test Guidelines, OPPTS 830.7840, Water Solubility; Column Elution Method, Shake Flask Method, 1998.

Method detail : A preliminary test indicated that the column elution method was appropriate. Glass beads (6.16 g) were weighed and placed in a glass vessel. Test item (0.12 g) was added and mixed thoroughly. No solvent was used. The carrier was poured into the elution column which was then filled with water. The system was equilibrated for approximately 2 hours. Elution of the test material from the carrier was performed using a circulation pump. Test temperature was 20°C. The flow rate was 0.56 mL/min in the first part of the test (about 98 hours) and 0.28 mL/min in the second part of the test (about 23 hours). The apparatus was run until equilibration of the saturation column was obtained, defined by at least five successive samples whose concentrations do not differ more than 30%. The column eluate was sampled at intervals of at least 1 hour to determine the concentration of cobalt, using atomic absorption spectroscopy.

Result : Based upon the results of 12 samples, the cobalt solubility was 4.6 mg/L (S.D. ± 0.4 mg/L), which corresponds to a water solubility of fatty acids, C9-

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**Remark** : C-13 neo, cobalt salts of 28.3 mg/L.  
: **Supporting data for dissociation products:**  
**Acid:** The water solubility for fatty acids, C9-C13 neo was determined at 20°C following Directive 84/449/EEC, A.6, to be 490 mg/L at pH 3 and 3800 mg/L at pH 7 (Appendix F, Part 1, IUCLID 2000 dataset).  
**Metal:** The reported water solubility for cobalt chloride is 450 g/L at 7°C (Appendix G).  
**Reliability** : [1] Reliable without restriction  
**Reference** : Tognucci, A., 2004. Determination of the water solubility of fatty acids, C9-C13-neo-cobalt salts. RCC Study No. 849106, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

### 2.7 FLASH POINT

**Type** :  
**Guideline/method** :  
**Value** : °C  
**Year** :  
**GLP** :  
**Test substance** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** :  
**Reliability** :  
**Reference** :

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### 3.1.1 PHOTODEGRADATION

Type	:			
Guideline/method	:			
Light source	:			
Light spectrum	:			
Relative intensity	:		based on	
Spectrum of substance	:	lambda (max, >295nm)	:	
		epsilon (max)	:	
		epsilon (295)	:	
Conc. of substance	:		at	°C
DIRECT PHOTOLYSIS				
Halflife (t1/2)	:			
Degradation	:	% after		
Quantum yield	:			
INDIRECT PHOTOLYSIS				
Sensitizer	:			
Conc. of sensitizer	:			
Rate constant	:			
Degradation	:			
Deg. product	:			
Year	:			
GLP	:			
Test substance	:			
Deg. products CAS#	:			
Method	:			
Method detail	:			
Result	:			
Remark	:			
Reliability	:			
Reference	:			

### 3.1.2 Dissociation

<b>Type</b>	: Dissociation constant determination
<b>Guideline/method</b>	: OECD 112
<b>pKa</b>	: 5.96 at 20°C
<b>Year</b>	: 2002
<b>GLP</b>	: Yes
<b>Test substance</b>	: Neo C9-13 Acid, Cobalt Salts, CAS no. 68955-83-9, received from OMG. Purple chunks, purity of 16.3% cobalt
<b>Approximate water solubility</b>	: 3.5 mg/L as determined by Inductively Coupled Plasma Atomic Emission Spectrometry in preliminary study
<b>Method</b>	: OECD Guideline 112, Dissociation Constants in Water
<b>Method detail</b>	: Three replicate samples of fatty acid, C9-13-neo-, cobalt salts were prepared at a nominal concentration of 1.5 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 1.0 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.0025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
<b>Result</b>	: Mean (N = 3) pKa value was 5.96 (SD = 0.0303) at 20°C
<b>Remark</b>	: The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

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**Reliability** : [1] Reliable without restriction.  
**Reference** : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of fatty acids, C9-13-neo-, cobalt salts, Wildlife International, Ltd. Study No. 534C-116, conducted for the Metal Carboxylates Coalition.

#### 3.2.1 MONITORING DATA

**Type of measurement** :  
**Media** :  
**Concentration** :  
**Substance measured** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** :  
**Reliability** :  
**Reference** :

#### 3.3.1 TRANSPORT (FUGACITY)

**Type** :  
**Media** :  
**Air** : % (Fugacity Model Level I)  
**Water** : % (Fugacity Model Level I)  
**Soil** : % (Fugacity Model Level I)  
**Biota** : % (Fugacity Model Level II/III)  
**Soil** : % (Fugacity Model Level II/III)  
**Year** :  
**Test substance** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** :  
**Reliability** :  
**Reference** :

#### 3.5 BIODEGRADATION

**Type** :  
**Guideline/method** :  
**Inoculum** :  
**Concentration** : related to  
related to  
**Contact time** :  
**Degradation** : (±) % after day(s)  
**Result** :  
**Kinetic of test subst.** : % (specify time and % degradation)  
%  
%  
%  
%  
**Control substance** :  
**Kinetic** : %  
%  
**Deg. product** :

### 3. Environmental Fate & Transport

ID 68955-83-9

Date November 7, 2005

Year :  
GLP :  
Test substance :  
Deg. products CAS# :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** Fatty acids, C9-C13 neo were not readily biodegradable. Approximately 2.3% was degraded over 28 days in a manometric respirometry test (OECD 301F). Exxon Biomedical Sciences, 1996. (Appendix F, Part 3, ExxonMobil Chemical Company, 2002). In the Biotic Degradation – Modified AFNOR Test (Directive 84/449/EEC, C.4), biodegradation of only 2% was observed after 28 days (Appendix F, Part 1, IUCLID Dataset 2000).  
**Metal:** Metal does not degrade.

Reliability :  
Reference :

#### 3.7 BIOCONCENTRATION

Type :  
Guideline/method :  
Species :  
Exposure period :  
Concentration :  
BCF :  
Elimination :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference :

at °C

## 4. Ecotoxicity

ID 68955-83-9

Date October 24, 2005

### 4.1 ACUTE TOXICITY TO FISH

Type :  
Guideline/method :  
Species :  
Exposure period :  
NOEC :  
LC0 :  
LC50 :  
LC100 :  
Other :  
Other :  
Other :  
Limit test :  
Analytical monitoring :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** Following Directive 84/449/EEC C.1, the 96-h LC50 for fatty acids, C9-C13 neo (as determined using water-accomodated fractions) was reported as 46 mg/L for the rainbow trout, *Onchorhynchus mykiss* (Appendix F, Part 1, IUCLID 2000 dataset).

**Metal:** For cobalt chloride, the 96-h LC50 was 1.41 mg Co/L for the highly sensitive rainbow trout, *Onchorhynchus mykiss*. Other fish species are less sensitive with 96-h LC50 values ranging from 22.0 to 333 mg Co/L (Appendix G).

Reliability :  
Reference :

### 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :  
Guideline/method :  
Species :  
Exposure period :  
NOEC :  
EC0 :  
EC50 :  
EC100 :  
Other :  
Other :  
Other :  
Limit test :  
Analytical monitoring :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** Following Directive 84/449/EEC C.2, the 48-h EC50 for fatty acids, C9-C13 neo (as determined using water-accomodated fractions) was

## 4. Ecotoxicity

ID 68955-83-9

Date October 24, 2005

reported as 41 mg/L for *Daphnia magna* (Appendix F, Part 1, IUCLID 2000 Dataset).

**Metal:** For cobalt chloride, the 48-h EC50 values for *Daphnia magna* have been reported as 1.52 mg Co/L and as 5.5 mg Co/L. For *Ceriodaphnia dubia*, 48-h LC50 values ranged from 2.35 to 4.60 mg Co/L (Appendix G).

Reliability :  
Reference :

### 4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :  
Guideline/method :  
Species :  
Endpoint :  
Exposure period :  
NOEC :  
LOEC :  
EC0 :  
EC10 :  
EC50 :  
Other :  
Other :  
Other :  
Limit test :  
Analytical monitoring :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** Following Directive 87/302/EEC, part C, p. 89, the 72-h EC50 for fatty acids, C9-C13 neo, (using water-accomodated fractions), was 55 – 160 mg/L, based on growth rate, for *Selenastrum capricornutum*. However, the pH was not adjusted so the effects are thought to be due to pH rather than the test substance. When the pH was adjusted, the EC50 was > 1000 mg/L (Appendix F, Part 1, IUCLID 2000 Dataset).

**Metal:** For cobalt chloride, the 96-h EC50 for *Chorella vulgaris* was 0.52 mg Co/L. For the duckweed *Lemna minor*, the 7-d IC50 was 16.9 mg Co/L, while for the blue-green alga *Spirulina platensis* the 96-h EC50 was 23.8 mg Co/L (Appendix G).

Reliability :  
Reference :

## 5. Toxicity

ID 68955-83-9

Date November 7, 2005

### 5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo :  
Type :  
Guideline/method :  
Species :  
Number of animals :  
    Males :  
    Females :  
Doses :  
    Males :  
    Females :  
Vehicle :  
Route of administration :  
Exposure time :  
Product type guidance :  
Decision on results on :  
    acute tox. tests :  
Adverse effects on :  
    prolonged exposure :  
Half-lives : 1<sup>st</sup>.  
                  2<sup>nd</sup>.  
                  3<sup>rd</sup>.  
Toxic behavior :  
Deg. product :  
Deg. products CAS# :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Metal:** Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal, with increasing solubility resulting in increasing absorption. Approximately 13-34% of cobalt chloride, a soluble form, is absorbed in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine. Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (Appendix G).

Reliability :  
Reference :

#### 5.1.1 ACUTE ORAL TOXICITY

Type :  
Guideline/Method :  
Species :  
Strain :  
Sex :  
Number of animals :  
Vehicle :  
Doses :

## 5. Toxicity

ID 68955-83-9

Date November 7, 2005

LD50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> For fatty acids, C9-C13, neo, the oral LD50 in rats (determined according to Directive 84/449/EEC B.1) was reported to be 2859 mg/kg (Appendix F, Part 1, IUCLID 2000 Dataset). <b>Metal:</b> For cobalt chloride hexahydrate, the oral LD50 in rats was 766 mg/kg (equivalent to 190 mg Co/kg). Other reported LD50s range from 19.8 to 85.5 mg Co/mg bw in rats. In mice, the LD50 for cobalt chloride was reported as 89.3 mg Co/kg bw (Appendix G).
Reliability	:	
Reference	:	

### 5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Metal:</b> No acute inhalation toxicity studies were located for cobaltous chloride (Appendix G).
Reliability	:	
Reference	:	

### 5.1.3 ACUTE DERMAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	

## 5. Toxicity

ID 68955-83-9

Date November 7, 2005

Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** The acute dermal LD50 for fatty acids, C9-C13, neo in the rat (determined according to Directive 84/449/EEC B.3) has been reported as >2000 mg/kg (Appendix F, Part 1, IUCLID 2000 Dataset).  
**Metal:** Increased proliferation of lymphatic cells was seen in rats, mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (Appendix G).

Reliability :  
Reference :

### 5.2.1 SKIN IRRITATION

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :  
Concentration :  
Exposure :  
Exposure time :  
Number of animals :  
Vehicle :  
Classification :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** Fatty acids, C9-C13, neo was classified as not irritating (Directive 84/449/EEC, B.4) to skin when tested on the rabbit (Appendix F, Part 1, IUCLID 2000 Dataset).  
**Metal:** Dermatitis is a common result of dermal exposure to cobalt in humans and is probably caused by an allergic reaction (Appendix G).

Reliability :  
Reference :

### 5.2.2 EYE IRRITATION

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :  
Concentration :  
Dose :  
Exposure time :  
Number of animals :  
Vehicle :  
Classification :  
Year :  
GLP :  
Test substance :  
Method :

## 5. Toxicity

ID 68955-83-9

Date November 7, 2005

Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> Fatty acids, C9-C13, neo was classified as not irritating (Directive 84/449/EEC, B.5) to the eyes of rabbits (Appendix F, Part 1, IUCLID 2000 Dataset).
Reliability	:	
Reference	:	

### 5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> Repeated dose toxicity of fatty acids, C9-C13, neo was determined according to Directive 92/69/EEC B.7. Administration by daily gavage over 4 weeks to rats resulted in a NOAEL of 300 mg/kg/bw and a LOAEL of >300 mg/kg bw. No adverse toxic effects were observed in any female treatment groups. In male rats, a dose-related hyaline droplet nephropathy was observed in the kidney of all treatment groups; this effect, however, is specific for young male rats and is not of toxicological relevance to humans (Appendix F, Part 1, IUCLID 2000 Dataset). <b>Metal:</b> Repeated oral dosing of rats with cobalt chloride hexahydrate for 8 weeks indicated the NOAEL was 0.6 mg Co/kg and the LOAEL was 2.5 mg Co/kg, based upon changes in hemoglobin content and numbers of erythrocytes. Another study reported oral doses of 0.5 and 2.5 mg Co/kg for 7 months stimulated hematopoiesis and decreased immunological reactivity in rats, while doses of 0.05 mg Co/kg had no effects. (Appendix G).
Reliability	:	
Reference	:	

### 5.5 GENETIC TOXICITY 'IN VITRO'

Type	:
Guideline/method	:
System of testing	:
Species	:
Strain	:

## 5. Toxicity

ID 68955-83-9

Date November 7, 2005

Test concentrations	:	
Cytotoxic concentr.	:	
Metabolic activation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<p><b>Supporting data for dissociation products:</b></p> <p><b>Acid:</b> Fatty acids, C9-C13, neo acid produced negative results in the bacterial gene mutation assay (Directive 92/69/EEC B13,B14) against four strains of <i>S. typhimurium</i> and one strain of <i>E. coli</i> when tested both with and without metabolic activation. When tested in a cytogenetic assay with Chinese hamster ovary cells, results were negative in the absence of metabolic activation but positive in the presence of S9. (Appendix F, Part 1, IUCLID 2000 Dataset).</p> <p><b>Metal:</b> Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt chloride, are generally non-mutagenic in bacterial assays, including plate incorporation and fluctuation assays with <i>Salmonella typhimurium</i> TA strains and <i>Escherichia coli</i> WP2. However, a weak positive mutagenic response has been found in the rec assay with <i>Bacillus subtilis</i> and in Chinese hamster V9 cells. DNA damage in isolated human lymphocytes was observed at 6.0 mg Co/L in the alkaline comet assay, and an increase in sister chromatid exchanges has been observed in human lymphocytes and macrophages (Appendix G).</p>
Reliability	:	
Reference	:	

### 5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	<p><b>Supporting data for dissociation products:</b></p> <p><b>Metal:</b> Oral administration of cobalt chloride hexahydrate to mice (20 – 80 mg.kg bw) produced a concentration-dependent increase in chromosomal aberrations. A dose-dependent increase in the incidence of micronucleated polychromatic erythrocytes was observed in mice subsequent to i.p. injection of <math>\text{CoCl}_2 \cdot 6\text{H}_2\text{O}</math>, at doses of 25 – 90 mg Co/kg bw. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL). (Appendix G).</p>
Remark	:	
Reliability	:	
Reference	:	

## 5. Toxicity

ID 68955-83-9

Date November 7, 2005

### 5.8.2 DEVELOPMENTAL TOXICITY

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :  
Route of admin. :  
Exposure period :  
Frequency of treatment :  
Duration of test :  
Doses :  
Control group :  
NOAEL maternal tox. :  
NOAEL teratogen. :  
Other :  
Other :  
Other :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

#### **Supporting data for dissociation products:**

**Metal:** In a developmental toxicity study with cobalt chloride exposure (5.4 to 21.8 mg Co/kg/day) in rats from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects were observed on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (Appendix G).

Reliability :  
Reference :

### 5.8.3 TOXICITY TO REPRODUCTION

Type :  
Guideline/method :  
In vitro/in vivo :  
Species :  
Strain :  
Sex :  
Route of admin. :  
Exposure period :  
Frequency of treatment :  
Duration of test :  
Doses :  
Control group :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :

## 5. Toxicity

ID 68955-83-9

Date November 7, 2005

Result  
Remark

:

:

**Supporting data for dissociation products:**

**Metal:** Cobalt exposure (as cobalt chloride hexahydrate in drinking water for 12 -13 weeks) affected male reproductive parameters for mice in a time- and dose-dependent manner. All dose levels (23.0 – 72.1 mg Co/kg-day) caused decreases in testicular weight and epididymal sperm concentration. Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (Appendix G).

Reliability  
Reference

:

:

### 6.0 OTHER INFORMATION

#### 6.1 CARCINOGENICITY

**Supporting data for dissociation products:**

**Metal:** The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). "No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt." (ATSDR Sept 2001 Draft, See Appendix G).

#### 6.2 Skin Sensitization

**Supporting data for dissociation products:**

**Acid:** Fatty acids, C9-C13, neo acid was not found to be sensitizing when tested on the guinea pig using the guinea pig maximization test (Directive 84/449/EEC, B.6). (Appendix F, Part 1, IUCLID 2000 Dataset).

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# I U C L I D

## D a t a s e t

Existing Chemical	Substance ID: 68938-07-8
CAS No.	68938-07-8
EINECS Name	Fatty acids, C9-13-neo-
EINECS No.	273-114-3
Molecular Formula	<no data>

Dataset created by: EUROPEAN COMMISSION - European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

Creation date: 19-FEB-2000

Number of Pages: 18

Chapters: all

Edition: Year 2000 CD-ROM edition

Flags: non-confidential

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European Chemicals Bureau

**1.0.1 OECD and Company Information**

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**Name:** EXXON CHEMICAL HOLLAND BV  
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**Name:** Shell Nederland Chemie B.V.  
**Street:** P.O. Box 3030  
**Town:** 3190 GH Hoogvliet-Rotterdam  
**Country:** Netherlands  
**Phone:** +31-10-2317005  
**Telefax:** +31-10-2317125

**1.0.2 Location of Production Site**

-

**1.0.3 Identity of Recipients**

-

**1.1 General Substance Information**

**Substance type:** organic  
**Physical status:** liquid

**1.1.1 Spectra**

-

**1.2 Synonyms**

Neo-acid 913

**Source:** EXXON CHEMICAL HOLLAND BV Botlek Rt.  
Exxon Chemical Belgium Antwerpen  
Deutsche Exxon Chemical G.m.b.H Koeln

Versatic 913 Distillate

**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

**1.3 Impurities**

-

**1.4 Additives**

-

**1.5 Quantity**

**Quantity** 5 000 - 10 000 tonnes

**1.6.1 Labelling**

-

**1.6.2 Classification**

-

**1.7 Use Pattern**

**Type:** type

**Category:** Non dispersive use

**Type:** type

**Category:** Use in closed system

**Type:** industrial

**Category:** Chemical industry: used in synthesis

**Type:** use

**Category:** Intermediates

**1.7.1 Technology Production/Use**

-

### 1.8 Occupational Exposure Limit Values

Type of limit:

Limit value:

Remark: None established.

Source: Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

### 1.9 Source of Exposure

-

### 1.10.1 Recommendations/Precautionary Measures

-

### 1.10.2 Emergency Measures

-

### 1.11 Packaging

-

### 1.12 Possib. of Rendering Subst. Harmless

-

### 1.13 Statements Concerning Waste

-

### 1.14.1 Water Pollution

-

### 1.14.2 Major Accident Hazards

-

### 1.14.3 Air Pollution

-

### 1.15 Additional Remarks

Remark: Not dangerous for conveyance under UN, IMO, ADR/RID and IATA/ICAO codes.

Waste/product disposal: recover or recycle if possible, otherwise incineration with wet scrubbing facilities.

Source: Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

### 1.16 Last Literature Search

-

**1.17 Reviews**

-

**1.18 Listings e.g. Chemical Inventories**

-

**2.1 Melting Point**

**Value:** < -20 degree C  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

**2.2 Boiling Point**

**Value:** ca. 195 - 280 degree C  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

**2.3 Density**

**Type:** relative density  
**Value:** .923 at 20 degree C  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

**2.3.1 Granulometry**

-

**2.4 Vapour Pressure**

**Value:** = .0065 hPa at 22.1 degree C  
**Method:** Directive 84/449/EEC, A.4 "Vapour pressure"  
**Year:** 1994  
**GLP:** yes  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(1)

**2.5 Partition Coefficient**

**log Pow:** = 3.05 - 3.17 at 20 degree C  
**Method:** OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"  
**Year:** 1994  
**GLP:** yes  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(2)

**2.6.1 Water Solubility**

**Value:** = .49 g/l at 20 degree C  
**Qualitative:** of very low solubility  
**pH:** = 3 and 20 degree C  
**Method:** Directive 84/449/EEC, A.6 "Water solubility"  
**Year:** 1994  
**GLP:** yes  
**Remark:** The product is a mixture of components. The value reported is the actual dissolved material when the medium is exposed to 10 g/l.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam (3)

**Value:** = 3.8 g/l at 20 degree C  
**Qualitative:** slightly soluble  
**pH:** = 7 and 20 degree C  
**Method:** Directive 84/449/EEC, A.6 "Water solubility"  
**Year:** 1994  
**GLP:** yes  
**Remark:** AS in record 1.  
At pH = 7 no saturation of the major components was reached at 10 g/l, as was at pH is 3.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam (4)

**2.6.2 Surface Tension**  
-**2.7 Flash Point**

**Value:** 114 degree C  
**Type:** closed cup  
**Method:**  
**Year:**  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

**2.8 Auto Flammability**

**Value:**  
**Remark:** Not applicable.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

**2.9 Flammability**

**Result:**  
**Remark:** Not applicable.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

### **2.10 Explosive Properties**

**Result:**

**Remark:** None.

**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

### **2.11 Oxidizing Properties**

**Result:**

**Remark:** None.

**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

### **2.12 Additional Remarks**

**Remark:** Viscosity at 25 degree C = 41.3 mm<sup>2</sup>/s.

**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

**3.1.1 Photodegradation**

-

**3.1.2 Stability in Water**

-

**3.1.3 Stability in Soil**

-

**3.2 Monitoring Data (Environment)**

-

**3.3.1 Transport between Environmental Compartments**

-

**3.3.2 Distribution**

-

**3.4 Mode of Degradation in Actual Use**

-

**3.5 Biodegradation**

**Type:** aerobic  
**Inoculum:** activated sludge, domestic, non-adapted  
**Concentration:** 60 mg/l related to Test substance  
**Degradation:** = 2 % after 28 day  
**Result:** under test conditions no biodegradation observed  
**Method:** Directive 84/449/EEC, C.4 "Biotic degradation - modified  
AFNOR test NF T90/302"  
**Year:** 1993 **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(5)

**3.6 BOD5, COD or BOD5/COD Ratio**

-

**3.7 Bioaccumulation**

-

**3.8 Additional Remarks**

-

**AQUATIC ORGANISMS****4.1 Acute/Prolonged Toxicity to Fish**

**Type:** semistatic  
**Species:** Oncorhynchus mykiss (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:**  
**LC50:** = 46  
**Method:** Directive 84/449/EEC, C.1 "Acute toxicity for fish"  
**Year:** 1994 **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** The change in the dissolved material are within the limit of acceptance (< 20 %m).  
The pH was 7.1  
The substances is a mixture of several components. As the concentration of the actual dissolved material changes in the loading rate, Water Accommodated Fractions (WAFs) have been used.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(6)

**4.2 Acute Toxicity to Aquatic Invertebrates**

**Species:** Daphnia magna (Crustacea)  
**Exposure period:** 48 hour(s)  
**Unit:** mg/l **Analytical monitoring:** yes  
**EC50:** = 41  
**Method:** Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"  
**Year:** 1994 **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** All remark of 4.1 reply here too  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(7)

**4.3 Toxicity to Aquatic Plants e.g. Algae**

**Species:** Selenastrum capricornutum (Algae)  
**Endpoint:** growth rate  
**Exposure period:** 72 hour(s)  
**Unit:** mg/l **Analytical monitoring:** yes  
**EC50:** = 55 - 160  
**Method:** Directive 87/302/EEC, part C, p. 89 "Algal inhibition test"  
**Year:** 1994 **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Note the remarks at item 4.1  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam  
**Test condition:** The pH was not adjusted. Therefore, the effects are thought to be due to the pH rather than the test substance. See also record 2.

(7)

#### 4. Ecotoxicity

date: 19-FEB-2000  
Substance ID: 68938-07-8

**Species:** Selenastrum capricornutum (Algae)  
**Endpoint:** growth rate  
**Exposure period:** 72 hour(s)  
**Unit:** mg/l **Analytical monitoring:** yes  
**EC50:** > 1000  
**Method:** Directive 87/302/EEC, part C, p. 89 "Algal inhibition test"  
**Year:** 1994 **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam  
**Test condition:** The pH was adjusted to 7.3 -8.4 at the start of the test.

(7)

#### 4.4 Toxicity to Microorganisms e.g. Bacteria

-

#### 4.5 Chronic Toxicity to Aquatic Organisms

##### 4.5.1 Chronic Toxicity to Fish

-

##### 4.5.2 Chronic Toxicity to Aquatic Invertebrates

-

#### TERRESTRIAL ORGANISMS

##### 4.6.1 Toxicity to Soil Dwelling Organisms

-

##### 4.6.2 Toxicity to Terrestrial Plants

-

##### 4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

-

##### 4.7 Biological Effects Monitoring

-

##### 4.8 Biotransformation and Kinetics

-

##### 4.9 Additional Remarks

-

**5.1 Acute Toxicity****5.1.1 Acute Oral Toxicity**

**Type:** LD50  
**Species:** rat  
**Sex:**  
**Number of Animals:**  
**Vehicle:**  
**Value:** 2859 mg/kg bw  
**Method:** Directive 84/449/EEC, B.1 "Acute toxicity (oral)"  
**Year:** GLP: yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(8)

**5.1.2 Acute Inhalation Toxicity**

-

**5.1.3 Acute Dermal Toxicity**

**Type:** LD50  
**Species:** rat  
**Sex:**  
**Number of Animals:**  
**Vehicle:**  
**Value:** > 2000 mg/kg bw  
**Method:** other  
**Year:** GLP: yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Test Guideline: Directive 84/449/EEC B3  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(8)

**5.1.4 Acute Toxicity, other Routes**

-

**5.2 Corrosiveness and Irritation**

**5.2.1 Skin Irritation**

**Species:** rabbit  
**Concentration:**  
  
**Exposure:**  
**Exposure Time:**  
**Number of**  
**Animals:**  
**PDII:**  
**Result:** slightly irritating  
**EC classificat.:** not irritating  
**Method:** Directive 84/449/EEC, B.4 "Acute toxicity (skin irritation)"  
**Year:** **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Mean of 24, 48 and 72 hour scores (N=3):  
Erythema 0.9  
Oedema 0.0  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(9)

**5.2.2 Eye Irritation**

**Species:** rabbit  
**Concentration:**  
**Dose:**  
**Exposure Time:**  
**Comment:**  
**Number of**  
**Animals:**  
**Result:** moderately irritating  
**EC classificat.:** not irritating  
**Method:** Directive 84/449/EEC, B.5 "Acute toxicity (eye irritation)"  
**Year:** **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Mean of 24, 48 and 72 hour scores (N=3):  
Redness 1.0  
Chemosis 0.3  
Opacity 1.3  
Iris 0.1  
There was a moderate initial pain reaction upon instillation into the eye.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(10)

### 5.3 Sensitization

**Type:** Guinea pig maximization test  
**Species:** guinea pig  
**Number of Animals:**  
**Vehicle:**  
**Result:** not sensitizing  
**Classification:** not sensitizing  
**Method:** Directive 84/449/EEC, B.6 "Acute toxicity (skin sensitization)"  
**Year:** **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** None of the 20 test animals showed a positive response at 24 or 48 hours after removal of the challenge patches.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(11)

### 5.4 Repeated Dose Toxicity

**Species:** rat **Sex:** male/female  
**Strain:** Sprague-Dawley  
**Route of admin.:** gavage  
**Exposure period:** 4 weeks  
**Frequency of treatment:** once daily  
**Post. obs. period:** none  
**Doses:** 0, 10, 55 300 mg/kg b.w./day  
**Control Group:** yes, concurrent vehicle  
**NOAEL:** 300 mg/kg bw  
**LOAEL:** > 300 mg/kg bw  
**Method:** other  
**Year:** **GLP:** yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Test guideline: Directive 92/69/EEC B7  
Vehicle: corn oil  
**Result:** No adverse toxic effects were observed in any of the female treatment groups. In male rats a dose-related hyaline droplet nephropathy was observed in the kidney of all treatment groups.  
Hyaline droplet nephropathy is a condition associated with alpha-2-microglobulin in the tubular epithelium of the kidney and is specific for young male rats; it is not of toxicological relevance to humans.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam

(12)

**5.5 Genetic Toxicity 'in Vitro'**

**Type:** Bacterial gene mutation assay  
**System of testing:** S. typhimurium TA1535, TA1537, TA98, TA100; E. coli WP2 uvrA pKM 101  
**Concentration:** 0, 31.25, 62.5, 125, 250, 500, 1000, 2000, 5000 microgram/plate  
**Metabolic activation:** with and without  
**Result:** negative  
**Method:** other  
**Year:** GLP: yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Solubility limited at concentrations of 2000 microgr/plate and above.  
Control substances confirmed the activity and sensitivity of the test system.  
Test guideline: Directive 92/69/EEC B13, B14  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam (13)

**Type:** Cytogenetic assay  
**System of testing:** Cultured Chinese hamster ovary cells (CHO-K1)  
**Concentration:** -S9: 13.67 - 250 microgr/mL | +S9: 100 - 1000 microgr/mL  
**Metabolic activation:** with and without  
**Result:** positive  
**Method:** other  
**Year:** GLP: yes  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Test guideline: Directive 92/69/EEC B10  
Test results were negative in the absence of S9. Control substances confirmed the activity and sensitivity of the test system.  
**Source:** Shell Nederland Chemie B.V. Hoogvliet-Rotterdam (14)

**5.6 Genetic Toxicity 'in Vivo'**  
-**5.7 Carcinogenicity**  
-**5.8 Toxicity to Reproduction**  
-**5.9 Developmental Toxicity/Teratogenicity**  
-

**5.10 Other Relevant Information**

-

**5.11 Experience with Human Exposure**

-

6. References

date: 19-FEB-2000  
Substance ID: 68938-07-8

- (1) Hazleton Europe Report No. 579/218-1014 To Shell Research.  
To be published, 1994.
- (2) Hazleton Europe Report No.: 579/218-1014 to Shell Research.  
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- (3) Hazleton Europe Report No.: 579/218-1014 to Shell Research.  
To be issued ,1994.
- (4) As in Record 1.
- (5) N.S. Battersby,  
Versatic 913D: An Assessment of Ready Biodegradability.  
Shell Group Research Report SBGR.93.275.  
Shell Research Ltd., Sittingbourne Kent UK, 1993
- (6) R. Toy,  
Versatic 913D: Acute Toxicity of Water Accommodated  
Fractions to Oncorhynchus Mykiss, Daphnia Magna and  
Raphidocelis Capitata.  
Shell Group Report: SBGR.94.037, in press.
- (7) As in 4.1.
- (8) Versatic 913D: Acute oral and dermal toxicity in rat, skin  
and eye irritancy in rabbit and skin sensitisation potential  
in guinea pig.  
Sittingbourne, Shell Research Ltd., SBGR.93.220, 1994
- (9) Versatic 913D: Acute oral and dermal toxicity in rat, skin  
and eye irritancy in rabbit and skin sensitisation potential  
in guinea pig.  
Sittingbourne, Shell Research Ltd. SBGR.93.220, 1994.
- (10) Versatic 913D: Acute oral and dermal toxicity in rat, skin  
and eye irritancy in rabbit and skin sensitisation potential  
in guinea pig.  
Sittingbourne, Shell Research Ltd., SBGR.93.220, 1994.
- (11) Versatic 913D: Acute oral and dermal toxicity in the rat,  
skin and eye irritancy in rabbit and skin sensitisation  
potential in guinea-pig.  
Sittingbourne, Shell Research Ltd. SBGR.93.330, 1994.
- (12) Versatic 913D: 28 day oral (gavage administration)  
sub-chronic toxicity study in the rat.  
The Hague, Shell Internationale Petroleum Maatschappij B.V.,  
HSE Report 94.10001, 1994.
- (13) Versatic 913D: Bacterial mutagenicity studies.  
Sittingbourne, Shell Research Ltd., SBGR.93.142, 1993.

6. References

date: 19-FEB-2000  
Substance ID: 68938-07-8

- (14) Versatic 913D: In-vitro chromosome studies using cultured Chinese hamster ovary cells.  
Sittingbourne, Shell Research Ltd., SBGR.93.326, 1994.

**7.1 Risk Assessment**

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HIGH PRODUCTION VOLUME (HPV)  
CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For The

NEOACIDS C5-C28 CATEGORY

CAS# 75-98-9: Propanoic acid, 2,2-dimethyl-  
CAS# 598-98-1: Propanoic acid, 2,2-dimethyl-, methyl ester  
CAS# 95823-36-2: Carboxylic acid, C6-8 neo  
CAS# 26896-20-8: Neodecanoic acid  
CAS# 68938-07-8: Fatty acids, C9-C13 neo  
CAS# 72480-45-6: Fatty acids, C9-C28 neo

Prepared by:

ExxonMobil Chemical Company

November 15, 2001  
Revised December 19, 2002

## **EXECUTIVE SUMMARY**

Under EPA's High Production Volume (HPV) Challenge Program ExxonMobil Chemical Company has committed to voluntarily compile a Screening Information Data Set (SIDS) on a category of chemicals defined as Neoacids C5-C28. This category is supported by the basic screening data needed for an initial assessment of the physicochemical properties, environmental fate, and human and environmental effects of chemicals as defined by the Organization for Economic Cooperation and Development (OECD). The information used to complete the HPV SIDS endpoints comes from existing data.

ExxonMobil Chemical Company believes a category of Neoacids C5-C28 is scientifically justifiable because their physicochemical and toxicological properties are very similar and follow a regular pattern as a result of the synthesis process. The structural similarities create a predictable pattern in the following parameters: physicochemical properties, environmental fate and effects, and human health effects. The similarities are based on the following:

- A common structure represented by R3CCOH,
- An incremental and constant change in carbon number across the category where the total number of carbons represented by R ranges from 3 to 26, and
- A likelihood of common precursors and breakdown products that can result in structurally similar metabolites (e.g. carboxylic acid).

This test plan is based on the observation that the toxicological properties are similar or vary in an incremental and predictable fashion within the category.

The test data compiled for the category anchor studies proves adequate to support a screening-level hazard assessment for the category and its members (CAS numbers, 75-98-9, 598-98-2, 95823-36-2, 26896-20-8, 68938-07-8, and 72480-45-6). The untested endpoints can be assessed by interpolation between data from the category anchor studies.

To complete the hazard assessment of the category, algal toxicity studies will be completed on both low and high molecular weight members of the category (75-98-9 and 72480-45-6 or 68938-07-8). Also, a fish acute and invertebrate toxicity study will be conducted on a high molecular weight member (68938-07-8).

Evaluation of the Neoacids C5-C28 as a category has several advantages. The category can be evaluated by using a matrix of completed anchor studies for various members of the category. By using this approach, the safety of the category can be determined without having to conduct tests for every end-point with every chemical. Not only will this inform the public earlier about any hazards of Neoacids C5-C28, but it will also reduce the number of animals that would be required to evaluate the toxicity of individual members of the Neoacids C5-C28 category.

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## TEST PLAN FOR NEOACIDS C<sub>5</sub>-C<sub>28</sub>

### I. INTRODUCTION

Under EPA's High Production Volume (HPV) Chemical Challenge Program ExxonMobil Chemical Company has committed to voluntarily compile a Screening Information Data Set (SIDS) on a category of chemicals defined as Neoacids C5-C28. This category is supported by the basic screening data needed for an initial assessment of the physicochemical properties, environmental fate, and human and environmental effects of chemicals as defined by the Organization for Economic Cooperation and Development (OECD). The information used to complete the HPV SIDS endpoints comes from existing data and fulfills an ExxonMobil obligation to the HPV Challenge Program.

ExxonMobil Chemical Company believes a category of Neoacids C5-C28 is scientifically justifiable because their physicochemical and toxicological properties are very similar and follow a regular pattern as a result of the synthesis process. The structural similarity of the component chemicals from these products creates a predictable pattern in the following parameters: physicochemical properties, environmental fate and effects, and human health effects. The similarities are based on the following:

- A common structure represented by R3CCOH,
- An incremental and constant change in carbon number across the category where the total number of carbons represented by R ranges from 3 to 26, and
- A likelihood of common precursors and breakdown products that can result in structurally similar metabolites (e.g. carboxylic acid).

This test plan is based on the observation that the toxicological properties are similar or vary in an incremental, predictable fashion within the category.

The test data compiled for the category proves adequate to support a hazard assessment for the category and its members (CAS numbers, 75-98-9, 598-98-2, 95823-36-2, 26896-20-8, 68938-07-8, and 72480-45-6) with the exception of few studies that have been identified as necessary to complete a thorough hazard dataset. Once all data are available, the untested endpoints can be assessed by interpolation between data from the category anchor studies. The existing data suggest that products in the Neoacids (C<sub>5</sub>-C<sub>28</sub>) Category exhibit relatively low toxicity for human health endpoints and moderate toxicity for the environmental health endpoints.

To complete the hazard assessment of the category, algal toxicity studies will be completed on the low and high molecular weight members of the category (75-98-9 and 72480-45-6 or 68938-07-8). Also, a fish acute and invertebrate toxicity study will be conducted on a high molecular weight member (68938-07-8).

The data from this category will be used to inform the public about the potential hazards of the Neoacids C5-C28. Developing a data matrix of anchor studies and applying justifiable read across practices will provide a sufficiently robust data set to characterize each endpoint in the HPV Chemical Challenge Program without having to conduct a test

for each endpoint and product. This resourceful use of existing data will result in fewer animals needed for testing purposes while adequately assessing the potential hazards of products in the Neoacids C5-C28 Category.

## II. CHEMICAL PROCESS AND DESCRIPTION

The Neoacids C5-C28 Category contains a group of neoacid products whose physicochemical and toxicological properties are very similar and follow a regular pattern as a result of synthesis and structural similarity (Table 1). The production of neoacid products involves the reaction between a branched olefin with carbon monoxide and water at elevated temperatures and pressures in the presence of an acid catalyst.

The category also contains propanoic acid, 2,2-dimethyl-, methyl ester (CAS#: 598-98-1). This material is an ester that is rapidly hydrolyzed to the parent neoacid - propanoic acid, 2,2-dimethyl- (CAS#: 75-98-9). Because of this rapid hydrolysis, propanoic acid, 2,2-dimethyl-, methyl ester has properties for health effects, aquatic toxicity, and environmental fate that are consistent with the neoacids.

The structural similarity of chemicals in this category creates a predictable pattern in the following parameters: physicochemical properties, environmental fate and effects, and human health effects. Neoacids are trialkylacetic acids in which each hydrogen on the non carboxyl carbon of acetic acid has been replaced by an alkyl group. The structural features of members of the category are as follows:

- A common structure - a quaternary carbon with the general structure  $R_3CCOOH$ ,
- An incremental and constant change across the category where R can be a branched alkyl group ranging from  $CH_3$  to  $C_6H_{13}$  as the main constituent,
- A likelihood of common precursors and breakdown products which result in structurally similar chemicals.

**Table 1. CAS Numbers and Descriptions**

CAS Number	Chemical Name
75-98-9	Propanoic acid, 2,2-dimethyl-
598-98-1	Propanoic acid, 2,2-dimethyl-, methyl ester
95823-36-2	Carboxylic acid, C6-8 neo*
26896-20-8	Neodecanoic acid
68938-07-8	Fatty acids, C9-13 neo
72480-45-6	Fatty acids, C9-28 neo

\* = Not currently HPV but included to facilitate category evaluation

The Neoacids C5-C28 category accomplishes the goal of the Challenge Program - to obtain screening level hazard information through the strategic selection of products to be tested within the category. The testing strategy is based on the principle that:

- These products behave in a similar or predictable manner, and
- Interpolation of data can be used to assess the neoacid products for which data are not available.

Procedures to assess the reliability of selected data for inclusion in this test plan are based on the guidelines described by Klimisch et al, 1997.

### III. TEST PLAN RATIONALE

#### A. Physicochemical Data

Physicochemical Data (i.e., melting point, boiling point, vapor pressure, water solubility, and Kow) for selected chemical components in the Neo Acid C5 - C28 Category were calculated using EPIWIN® model (EPIWIN, 1999), as discussed in the EPA document entitled "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program." These data will be presented as ranges, based on the chemical components selected to represent each neoacid product. In addition, measured data for some of these endpoints will also be provided for selected neoacid products where readily available. Where possible, measured and calculated data will be presented together for comparison purposes.

Table 2 lists selected measured physicochemical data (melting point, boiling point, and vapor pressure) as they appear on the material safety data sheets for products in this category. These data are provided with this test plan to further justify these products as a distinct category under the HPV Chemical Challenge Program. Also included are calculated values for water solubility and K<sub>ow</sub>. As shown by the data in Table 2, the structural similarity of the neoacid products results in a predictable and incrementally increasing pattern of physiochemical properties from the C5 to C9-28 products.

**Table 2. Selected Physical Properties of Neoacids (C<sub>5</sub>-C<sub>28</sub>)**

CAS NUMBER	CHEMICAL NAME	MELTING POINT (° C)	BOILING POINT (° C)	WATER SOLUBILITY mg/L	VAPOR PRESSURE (mm Hg @ 25° C)	Log Kow
75-98-9	Propanoic acid, 2,2-dimethyl- (C5)	35 <sup>a</sup>	163.8 <sup>a</sup>	15,590	1.54	1.5 <sup>a</sup>
598-98-1	Propanoic acid, 2,2,-dimethyl-, methyl ester (C6)	-62.5	101 <sup>a</sup>	2,835	35.7	1.8 <sup>a</sup>
95823-36-2	Carboxylic acid, C6-8 neo (C7)	24.6	207.8	1912	0.244	2.4
26896-20-8	Neodecanoic acid (C10)	57.1	262.4	69	0.0071	3.9
68938-07-8	Fatty acids, C9-13 neo	37 - 76	234 - 291	3.1 - 243	0.001 - 0.046	3.3 - 5.2
72480-45-6	Fatty acids, C9-28 neo	37 - 204	234 - 504	<1 - 243	<1.7 E <sup>-12</sup> - 0.046	3.3 - 6.0

<sup>a</sup> Measured values supplied by experimental database in EPIWIN

## **B. Human Health Effects**

The structural similarity of the Neoacids C5-C28 influences both their physicochemical (Table 2) and their toxicological properties (Sections C and D). As a chemical category, the Neoacids C5-C28 have predictable, low-level environmental and health hazards.

ExxonMobil Chemical Company believes the category of Neoacids C5-C28 is scientifically justifiable and that the test data compiled for the category proves adequate to support a screening-level hazard assessment for the category and its members (CAS numbers, 75-98-9, 598-98-2, 95823-36-2, 26896-20-8, 68938-07-8, and 72480-45-6). One can assess the untested endpoints by extrapolation between and among the category members. The proposed category assessment plan is shown in Table 3.

### **Metabolism**

Propanoic acid, 2,2-dimethyl-, methyl ester is rapidly cleaved to Propanoic acid, 2,2-dimethyl-. Due to the stability conferred by the quaternary carbon, Neoacids C5-C28 are relatively resistant to biotransformation and do not readily form bioactive metabolites. Enzymatic removal of the alkyl groups at the quaternary carbon would allow for other metabolic processes to occur. These would likely be mitochondrial beta-oxidation or by cytochrome P450 mediated omega and omega-minus-one oxidation (may be followed by beta-oxidation) to produce acetate. However, since Neoacids C5-C28 are not readily metabolized, they would primarily be eliminated in the urine as glucuronic acid conjugates or by dealkylation (Katz and Guest, 1994).

## **C. Presentation of Neoacids C5-C28 Category Health Effects Data Associated with the Anchor Studies under the HPV Challenge Program**

### **Acute Oral Toxicity**

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
ACUTE ORAL - RAT	= 2000 mg/kg	RA	1860 mg/kg	= 2000 mg/kg	RA	RA

All of the Neoacids C5-C28 have a low order of toxicity to rats via the oral route of exposure (EBSI, 1964). The LD<sub>50</sub> values for Propanoic acid, 2,2-dimethyl- and Neodecanoic acid were 2000 mg/kg. In addition, the LD<sub>50</sub> for Carboxylic acid, C6-8 neo was 1860 mg/kg. These results demonstrate that members of the Neoacids C5-C28 Category have a consistent, low order of acute oral toxicity.

## Acute Dermal Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
ACUTE DERMAL - RABBIT	= 3160 mg/kg	RA	> 3160 mg/kg	> 3160 mg/kg	RA	RA

The Neoacids C5-C28 have a low order of toxicity via the dermal route of exposure (EBSI, 1964). The rabbit dermal LD<sub>50</sub> for all members of the category was equal to or greater than 3160 mg/kg. This indicates that the members of this category have a consistent pattern of acute toxicity via the dermal route of exposure.

## Genotoxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
AMES - S. typhimurium; TA98, 100, 1535, 1537, 1538 ± Activation	D	RA	RA	D	D	RA
Chromosomal Aberration - In Vitro or In Vivo	D	RA	RA	D	D	RA

RA Read Across

D Data available from another source, robust summaries will be submitted when they become available

There are no structural alerts to suggest that Neoacids C5-C28 are likely to be genotoxic. In addition, it has come to our attention that another producer of these materials has genetic toxicology data available. These data include both mutagenicity and chromosomal aberration studies on several members of the category. Pending our receipt and review of these studies, we will re-evaluate the need to do genetic toxicology testing. However, we do not anticipate that any additional genotoxicity testing will be required. We will submit additional robust summaries once this information is available to us.

## Subchronic Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
RAT DERMAL	NOAEL (dermal) = 300 mg/kg	RA	NOAEL (dermal) = 553.7 mg/kg	NOAEL (dermal) = 2280 mg/kg	RA	RA

The subchronic toxicity of Neoacids C5-C28 has been assessed by conducting repeat dermal exposure studies. Dermal exposure is the primary route of exposure for Neoacids C5-C28, particularly in an industrial setting. An evaluation of the repeated dose studies indicates that Neoacids C5-C28 have a low order of subchronic toxicity. Propanoic acid, 2,2-dimethyl-, in isopropyl alcohol solution, was repeatedly applied to the shaved intact skin of albino rabbits 5 days/week for two weeks (for a total of 10 applications) at doses of 30 or 300 mg/kg/day (Hazleton, 1964a). Slight to moderate irritation at the low dose and moderate to marked irritation at the high dose was observed. Slight or moderate erythema, atonia, and desquamation were seen at the low dose. At the high dose, skin irritation consisted of moderate erythema, slight to marked edema, moderate or marked atonia and desquamation. Some dermal necrosis at the site of application was seen in three rabbits and persisted throughout the study. Control animals that received only the solvent (isopropyl alcohol) showed slight irritation. There were no signs of systemic toxicity attributable to dermal absorption of propanoic acid, 2,2-dimethyl-. The NOAEL for systemic toxicity in this study was 300 mg/kg.

In a similar study, carboxylic acid, C6-8 neo was applied at 55.4 mg/kg and 553.7 mg/kg for 10 applications (Hazleton, 1964b). No treatment related effects were observed on behavior of clinical signs during the in-life phase of the study. Gross pathology of the animals in all dose groups did not reveal any abnormalities. Repeated application of carboxylic acid C6-8 neo did produce marked skin irritation with some dermal necrosis at the site of application in the high dose group. Since no systemic effects were observed in this study, the NOAEL for systemic effects following subchronic dermal application of carboxylic acid, C6-8 neo was 553.7 mg/kg.

Repeated dermal application (400 or 2800 mg/kg daily for a total of 10 applications) of undiluted Neodecanoic acid generally produced irritation at the low dose and fissuring at the high dose (Hazleton, 1964c). Slight to moderate erythema, atonia and desquamation were seen at the low dose. At the high dose, skin irritation consisted of moderate erythema, moderate to severe atonia, and desquamation with fissuring. No signs of systemic toxicity were attributed to Neodecanoic acid. Therefore, the NOAEL for systemic toxicity following subchronic dermal application of Neodecanoic acid was 2280 mg/kg.

In summary, Neoacids C5-C28 have a low order of subchronic toxicity. In addition, they display a consistent pattern of subchronic toxicity in that the NOAEL for systemic toxicity increases in a predictable pattern from the low to the high molecular weight end of the category. Therefore, Neoacids C5-C28 do not require further testing to assess subchronic toxicity.

## Developmental Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
DEVELOPMENTAL ORAL - RAT	RA	RA	NOAEL maternal = 250 mg/kg NOAEL fetal = 250 mg/kg  NOAEL (isooctanoic) maternal = 400 mg/kg NOAEL fetal = 800 mg/kg  NOAEL (isooctanoic acid) = 7500 ppm in diet	NOAEL parental = 1500 ppm in diet NOAEL F1 = 1500 ppm NOAEL F2 = 1500 ppm	NOAEL (isononanoic acid) = 1200 ppm in diet	RA

The potential for developmental toxicity of Neoacids C5-C28 can be assessed by evaluating the available data on neoacids as well as by comparison to the data on isoacids and structure-teratogenicity relationships. The available developmental toxicity data on neoacids indicate that they are not selective developmental toxicants. A developmental toxicity study conducted on Carboxylic acid, C6-8 neo produced a NOAEL of 250 mg/kg for both maternal and fetal effects (EBSI, 1986). Carboxylic acid, C6-8 neo was not a selective developmental toxicant in this study. In a 3-generation reproduction study with Neodecanoic acid, developmental effects were not observed in either the F1 or F2 offspring (Hazleton, 1968). This study produced a NOAEL of 1500 ppm (in diet) for the maternal, F1, and F2 generations.

Additional developmental toxicology data are available for isoacids, which are isomers of the neoacids. The isoacids are aliphatic carboxylic acids that have saturated branching structures. Isooctanoic acid was tested for developmental toxicity in female rats at doses of 0, 200, 400, and 800 mg/kg/day during gestation days 6 - 15 (EBSI, 1995). At 800 mg/kg/day, maternal toxicity was observed; however, there were no effects at 400 mg/kg/day. There were no biologically significant developmental effects in this study. The no-observable-adverse-effect level (NOAEL) for maternal toxicity was 400 mg/kg/day and for developmental toxicity was 800 mg/kg/day.

In a one-generation reproductive toxicity range-finding study, rats were exposed to isooctanoic acid at dietary levels of 1000, 5000, 75000, or 10,000 ppm (EBSI, 1999). In the parental generation, there were no treatment-related effects on survival, organ weights, or reproductive function. In the offspring, there were no treatment-related effects on survival, developmental landmarks, or any significant findings in postmortem evaluations. Statistically significant decreases in the mean offspring body weights of males and females were observed at 10,000 ppm. The high dose also resulted in a

suppression of body weight gain in the adult females. Thus, the NOAEL for both parental and offspring effects was 7500 ppm.

A one-generation reproduction study was conducted on isononanoic acid (EBSI, 1998). Rats were administered the test material in the diet at doses of 0, 600, 1200, 2500, and 5000 ppm. There were no treatment-related effects observed on mating, fertility, fecundity, or gestation indices or during sperm analysis. Evidence of maternal toxicity included decreased body weights and increased liver weights in the 2500 and 5000 ppm dose groups. In the offspring, reduced survival indices were noted in the 5000 ppm dose group, and reduced body weights were noted in the 2500 and 5000 ppm dose groups. The NOAEL for both maternal and offspring effects in this study was 1200 ppm.

Further support for the evaluation of the potential of neoacids to be developmental toxicants comes from an analysis of the structure activity relationships that affect teratogenicity. A structure-teratogenicity analysis of carboxylic acids concluded that aliphatic acids, which have a dimethyl substitution at the C-2 position, are not developmental toxicants (Di Carlo, 1990). Furthermore, the structural requirements for carboxylic acid teratogenicity require an alpha hydrogen and a free carboxylic group. Since the neoacids are defined by their trialkyl substitution at the alpha carbon, there is no alpha hydrogen. In addition, steric hindrance of the carbonyl group by the quaternary center of the alpha carbon inhibits reactions.

In conclusion, the available test data on neoacids and their isomers, as well as the structure-teratogenicity relationship for aliphatic acids, provide sufficient information for a screening-level assessment of the developmental toxicity of neoacids. Based on these analyses, neoacids are not considered to be selective developmental toxicants and no further testing is proposed.

## Reproductive Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
REPRODUCTIVE ORAL - RAT	RA	RA	NOAEL (isooctanoic acid) = 7500 ppm in diet	NOAEL parental = 1500 ppm in diet NOAEL F1 = 1500 ppm NOAEL F2 = 1500 ppm	NOAEL (isononanoic acid) = 1200 ppm in diet	RA

The available reproductive toxicity studies and developmental toxicity studies prove adequate to support a screening-level hazard assessment for the reproductive toxicity potential of Neoacids C5-C28. These data support the conclusion that the Neoacids C5-C28 are not selective reproductive toxicants.

In a modified three-generation reproduction study, rats were exposed to 100, 500, or 1500 ppm Neodecanoic acid in the diet (approximately 5, 25 and 75 mg/kg/day, respectively) (Hazleton, 1968). No significant effects were observed in survival, appearance, behavior, or reproductive performance of the parents. No adverse effects were demonstrated in offspring on growth, appearance, or behavior. No treatment related effects were observed at gross or microscopic pathology. The NOAEL in this study was greater than 1500 ppm. The data indicate that Neodecanoic acid is not a reproductive toxicant.

In a one-generation reproductive toxicity range-finding study, rats were exposed to isooctanoic acid at dietary levels of 1000, 5000, 75000, or 10,000 ppm (EBSI, 1999). In the parental generation, there were no treatment-related effects on survival, organ weights, reproductive function, or sperm indices. In the offspring, there were no treatment-related effects on survival, developmental landmarks, or any significant findings in postmortem evaluations. Statistically significant decreases in the mean offspring body weights of males and females were observed at 10,000 ppm. The high dose also resulted in a suppression of body weight gain in the adult females. Thus, the NOAEL for both parental and offspring effects was 7500 ppm.

A one-generation reproduction study was also conducted on isononanoic acid (EBSI, 1998). Rats were administered the test material in the diet at doses of 0, 600, 1200, 2500, and 5000 ppm. There were no treatment-related effects observed on mating, fertility, fecundity, or gestation indices or during sperm analysis. Evidence of maternal toxicity included decreased body weights and increased liver weights in the 2500 and 5000 ppm dose groups. In the offspring, reduced survival indices were noted in the 5000 ppm dose group, and reduced body weights were noted in the 2500 and 5000 ppm dose groups. The NOAEL for both maternal and offspring effects in this study was 1200 ppm.

In summary, these data prove adequate to support a screening level assessment of the reproductive toxicity of Neoacids C5-C28. Furthermore, these data indicate that Neoacids C5-C28 have a low order of reproductive toxicity.

#### **D. Aquatic Toxicity**

The neoacid products ranging from Propanoic acid, 2,2-dimethyl- to fatty acids, C9-13 neo, have been shown to produce an expected increasing level of acute toxicity to freshwater fish and invertebrates. This is based on data from the literature that are used to read across to selected neoacid products in this test plan and company data specifically for products in this category. Although there are insufficient data to confirm that a similar pattern of alga toxicity exists, based on the fish and invertebrate data, a similar increasing level of toxicity is expected from the lower to higher carbon numbered products. Proposed testing will develop the data needed to confirm this expectation. Based on the existing data, products in the Neoacids (C<sub>5</sub>-C<sub>28</sub>) Category demonstrate a low to moderate degree of aquatic toxicity from the low to high carbon numbered products, respectively.

## Fish Acute Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C7)	Carboxylic acid, C6-8 neo (C6-8)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
<b>FISH ACUTE TOXICITY (96-hour, mg/L)</b>	380	RA	630*	37.2	TESTING PROPOSED	RA

RA read across

\* Data are for a C7 branched and linear aliphatic acid product that does not contain a quaternary carbon, but is used to read across to a C6-8 neoacid product

Acute experimental fish toxicity tests are reported for Rainbow Trout (*Oncorhynchus mykiss*) and Goldfish (*Carassius auratus*). The results show that a C5 neo acid, C7 linear and branched aliphatic acid (used as read across to the C6-8 neo acid), and C10 neo acid products demonstrate that these products have a potential to cause acute fish toxicity (96-hour LC50) in the range of 630 to 37.2 mg/L. (Bridie 1979, EBSI 1993c, EBSI 1996b). The C9-13 neoacid, and the C9-28 neoacid products are not characterized. Therefore, to adequately assess the potential toxicity of the Neoacids (C<sub>5</sub>-C<sub>28</sub>) Category to fish, an acute toxicity test with the fatty acids, C9-13, neo, product will be conducted. The data from this study will be used to read across to the fatty acids, C9-28, neo, product. Comparable toxicity is expected for these two products because the higher molecular weight fatty acid components in the C9-28 neo acid product have extremely low water solubilities and do not have the potential to be in solution at effect causing levels, unlike the lower molecular weight components whose water solubilities are sufficient to cause an effect as demonstrated by the C10 neoacid product.

## Invertebrate Acute Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C7)	Carboxylic acid, C6-8 neo (C6-8)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
<b>DAPHNID ACUTE TOXICITY (48-hour, mg/L)</b>	203	RA	138*	47.1	TESTING PROPOSED	RA

RA read across

\*Data are for a C7 branched and linear aliphatic acid product that does not contain a quaternary carbon, but is used to read across to a C6-8 neoacid product

Acute experimental toxicity studies are reported for the Daphnid (*Daphnia magna*). The results show that a C5 neo acid, C7 linear and branched aliphatic acid (used as read across to the C6-8 neo acid), and C10 neo acid product have the potential to cause

acute toxicity (48 hour EL50 or EC50) in the range of 203 to 47.1 mg/L (EG&G 1977a, EG&G 1977b, EBSI 1993a). The C9-13 neoacid, and the C9-28 neoacid products are not characterized. Therefore, to adequately assess the potential toxicity of the Neoacids (C<sub>5</sub>-C<sub>28</sub>) Category to the Daphnid, an acute toxicity test with the fatty acids, C9-13, neo, product will be conducted. The data from this study will be used to read across to the fatty acids, C9-28, neo, product. Comparable toxicity is expected for these two products because the higher molecular weight fatty acid components in the C9-28 neo acid product have extremely low water solubilities and do not have the potential to be in solution at effect causing levels, unlike the lower molecular weight components whose water solubilities are sufficient to cause an effect as demonstrated by fish and invertebrate toxicity data for the C10 neoacid product.

### Alga Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C7)	Carboxylic acid, C6-8 neo (C6-8)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
<b>ALGA TOXICITY</b> (96-hour, mg/L)	TESTING PROPOSED	RA	6.5 (2)*	RA	TESTING PROPOSED	RA

(1) biomass  
(2) growth rate  
RA read across

\*Data are for a C7 branched and linear aliphatic acid product that does not contain a quaternary carbon, but is used to read across to a C6-8 neoacid product

An acute experimental toxicity value is reported for the freshwater alga (*Selenastrum capricornutum*) for a C7 linear and branched aliphatic acid product that is used as read across data to the C7 neoacid. This result shows that a C7 acid product has the potential to cause toxicity (72 hour EC50) at a concentration of 6.5 mg/L, based on alga growth rate (EBSI 1993b). Although there are no data for the remaining neoacid and neoacid ester products, overall, they are expected to exhibit a range of toxicity that falls above and below the value for the C7 aliphatic acid product. To adequately assess the potential toxicity of the Neoacids (C<sub>5</sub>-C<sub>28</sub>) Category to an alga, toxicity tests with a C5 neoacid and fatty acids, C9-13, neo, product will be conducted. The data from the fatty acids, C9-13, neo, product will be used to read across to the fatty acids, C9-28, neo, product. Comparable toxicity is expected for these two products because the higher molecular weight fatty acid components in the C9-28 neo acid product have extremely low water solubilities and do not have the potential to be in solution at effect causing levels, unlike the lower molecular weight components whose water solubilities are sufficient to cause an effect as demonstrated by the C10 neoacid product.

## E. Environmental Fate

Biodegradation data are available for three neoacid products. They show that neoacid products do not have the potential to biodegrade to a great extent within a standard 28-day test duration.

Although there is some information on photodegradation and fugacity, a complete data set to adequately characterize the neoacid products does not exist. Chemical equilibrium models are used to calculate fugacity, which describes the potential of a chemical to partition in the environment. These data can only be calculated. Preliminary information for selected component chemicals of products in the Neoacids (C<sub>5</sub>-C<sub>28</sub>) Category suggests that these products are expected to partition primarily to water and soil. However, their fate in air is of environmental interest (this is discussed below under photodegradation). In addition, the majority of the component chemicals in these products have relatively low K<sub>ow</sub> values, which suggests that they will not tend to partition to suspended organic matter in air and precipitate to aquatic and terrestrial environmental compartments to a significant extent.

### Biodegradation

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C7)	Carboxylic acid, C6-8 neo (C6-8)	Neodecanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
28-Day Aerobic Biodegradation Test	24.1 %ThOD	RA	44.0 %ThOD	11 % ThOD	2.3 % ThOD	RA

RA read across

The existing biodegradation data for the neoacids products suggest that these products will not degrade rapidly in the environment. Four products have been tested and they exhibited an extent of biodegradation that ranged from approximately 2 to 44% after 28 days incubation (EBSI 1996a). These data were generated using a closed system with non-acclimated inocula. The test systems were continuously stirred, which is recommended when evaluating mixtures with several components, some of which have minimal water solubility.

### Photodegradation – Photolysis

Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. Simple chemical structures can be examined to determine whether a chemical has the potential for direct photolysis in

water. First order reaction rates can be calculated for some chemicals that have a potential for direct photolysis using the procedures of Zepp and Cline (Zepp, 1977). UV light absorption of the chemical components in this category will be evaluated to identify those having the potential to degrade in solution. For those compounds with a potential for direct photolysis in water, first order reaction rates will be calculated. A technical document will be prepared that summarizes the results of information developed for this endpoint.

### **Photodegradation – Atmospheric Oxidation**

Photodegradation can be measured (US EPA, 1999a) (EPA identifies OECD test guideline 113 as a test method) or estimated using models accepted by the EPA (US EPA, 1999b). An estimation method accepted by the EPA includes the calculation of atmospheric oxidation potential (AOP).

Atmospheric oxidation as a result of hydroxyl radical attack (OH<sup>-</sup>) is not direct photochemical degradation, but rather indirect degradation. AOPs can be calculated using a computer model. Neoacid products, such as those in the Neoacid (C<sub>5</sub>-C<sub>28</sub>) Category, have a lower potential to volatilize to air. In air, these chemicals may undergo reaction with photosensitized oxygen in the form of ozone and hydroxyl radicals.

The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPIWIN, 1999) is used by OPPTS (Office of Pollution Prevention and Toxic Substances). This program calculates a chemical half-life based on an overall OH<sup>-</sup> reaction rate constant, a 12-hr day, and a given OH<sup>-</sup> concentration. This calculation will be performed for the representative chemical components in the Neoacids (C<sub>5</sub>-C<sub>28</sub>) Category and summarized in robust summaries for this group of products.

### **Stability in Water (Hydrolysis)**

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Neely, 1985). Stability in water can be measured (US EPA, 1999a) (EPA identifies OECD test guideline 111 as a test method) or estimated using models accepted by the EPA (US EPA, 1999b).

All of the chemical structures included in this category are neoacids with the exception of propanoic acid, 2,2-dimethyl-, methyl ester (C<sub>6</sub> neoacid methyl ester), which is a carboxylic acid ester. The neoacid products are not expected to hydrolyze at a measurable rate. A technical document will be prepared that discusses the nature of the chemical bonds present and the potential reactivity of this group of chemicals with water. The computer model Hydrowin version 1.67 (EPIWIN 1999) will be used to calculate the potential hydrolysis rate for the C<sub>6</sub> neoacid methyl ester. This information will be summarized in robust summaries for this group of products.

## **Chemical Transport and Distribution In The Environment (Fugacity Modeling)**

Fugacity based multimedia modeling can provide basic information on the relative distribution of chemicals between selected environmental compartments (i.e., air, soil, sediment, suspended sediment, water, biota). The US EPA has acknowledged that computer modeling techniques are an appropriate approach to estimating chemical partitioning (fugacity is a calculated endpoint and is not measured). A widely used fugacity model is the EQC (Equilibrium Criterion) model (Mackay, 1996). EPA cites the use of this model in its document titled *Determining the Adequacy of Existing Data* (US EPA, 1999a), which was prepared as guidance for the HPV Program.

In its document, EPA states that it accepts Level I fugacity data as an estimate of chemical distribution values. The input data required to run a Level I model include basic physicochemical parameters; distribution is calculated as percent of chemical partitioned to 6 compartments (air, soil, water, suspended sediment, sediment, biota) within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical is likely to partition.

The EQC Level I is a steady state, equilibrium model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment. This model will be used to calculate distribution values for representative chemical components identified in products in this category. A computer model, EPIWIN – version 3.02 (EPIWIN, 1999), will be used to calculate the properties needed to run the Level I EQC model. This information will be summarized in robust summaries for this group of products.

## **IV. TEST PLAN SUMMARY**

ExxonMobil Chemical Company believes that the Neoacids C5-C28 Category of chemicals should be further examined in the following manner:

- Conduct Ames assays on Propanoic acid, 2-2-dimethyl- (CAS# 75-98-9) and Neodecanoic acid (CAS# 26898-20-8) to evaluate the mutagenic potential of Neoacids C5-C28.
- Conduct mouse micronucleus assays Propanoic acid, 2-2-dimethyl- (CAS# 75-98-9) and Neodecanoic acid (CAS# 26898-20-8) to evaluate the clastogenic potential of Neoacids C5-C28.
- Calculate physicochemical data as described in the EPA document titled, *The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program* for selected chemical components of the neo acid products in this category. Provide measured data for selected products where readily available.

- Prepare a technical discussion on the potential of neo acid products in this category to photodegrade. Calculate AOP values for selected chemical components of neoacid products in this category.
- Prepare a technical discussion on the potential of neo acid products in this category to hydrolyze. Calculate the hydrolysis rate of Propanoic acid, 2,2-dimethyl-, methyl ester (CAS# 598-98-1).
- Calculate fugacity data for selected chemical components of neo acid products in this category.
- Conduct a fish acute toxicity test with Fatty acids, C9-13 neo (CAS# 68938-07-8).
- Conduct a Daphnid acute toxicity test with Fatty acids, C9-13 neo (CAS# 68938-07-8).
- Conduct algal toxicity tests with Propanoic acid, 2-2-dimethyl- (CAS# 75-98-9) and Neodecanoic acid (CAS# 26898-20-8).

ExxonMobil Chemical Company believes the thorough evaluation of the strategic anchor studies, the development of selected information and data, and the overall robustness of the final screening data set for the Neoacids C5-C28 Category complies with the objectives of the HPV volunteer testing program.

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**Table 3. Assessment Plan for the Neoacids C5-C28 Category Under the Program.**  
**(Robust summaries for existing studies are submitted separately.)**

Stream Description	Human Health Effects						Ecotoxicity			Physical Chem. <sup>1</sup>	Environmental Fate			
	Acute Toxicity	Genetic Point Mut.	Genetic Chrom.	Sub-chronic	Developmental	Reproduction	Acute Fish	Acute Invert.	Algal Toxicity		Photo-deg.	Hydrolysis	Fugacity	Biodeg.
Propanoic acid, 2,2-dimethyl-	A	D	D	A	RA	RA	A	A	T	CM/M	CM	CM	CM	A
Propanoic acid, 2,2-dimethyl-, methyl ester	RA	RA	RA	RA	RA	RA	RA	RA	RA	CM/M	CM	CM	CM	RA
Carboxylic acid, C6-8 neo	A	RA	RA	A	A	RA isooctanoic	A	A	A	CM/M	CM	CM	CM	A
Neodecanoic acid	A	D	D	A	RA	A	A	A	RA	CM/M	CM	CM	CM	A
Fatty acids, C9-13 neo	RA	D	D	RA	RA	RA isononanoic	T	T	T	CM/M	CM	CM	CM	A
Fatty acids, C9-28 neo	RA	RA	RA	RA	RA	RA	RA	RA	RA	CM/M	CM	CM	CM	RA

1 Measured data for selected physicochemical endpoints will be identified in conjunction with calculated data to characterize this category.

A	Adequate existing data available	TD	Technical Discussion proposed	RA	Read Across (see Sec. III.B)
CM	Computer Modeling proposed	T	Testing proposed	M	Measured data where available
NA	Not Applicable	D	Data available from another supplier; robust summaries will be provided		

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**Robust Summaries  
(Mammalian Toxicity)**

CAS# 75-98-9: Propanoic acid, 2,2-dimethyl-  
CAS# 598-98-1: Propanoic acid, 2,2-dimethyl-, methyl ester  
CAS# 95823-36-2: Carboxylic acid, C6-8 neo  
CAS# 26896-20-8: Neodecanoic acid  
CAS# 68938-07-8: Fatty acids, C9-C13 neo  
CAS# 72480-45-6: Fatty acids, C9-C28 neo

Prepared by:

ExxonMobil Chemical Company

November 15, 2001

(Revised December 17, 2002)

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CAS # 75-98-9; Propanoic acid, 2,2-dimethyl-

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- Acute Dermal
- Acute Inhalation
- Repeat Dose - Dermal

CAS # 95823-36-2; Carboxylic acid, C6-8 neo

- Acute Oral
- Acute Dermal
- Acute Inhalation
- Repeat Dose - Dermal
- Developmental Toxicity

CAS #26896-20-8; Neodecanoic acid

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CAS # 25103-52-0; Isooctanoic acid (read-across)

- Developmental Toxicity
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CAS #3302-10-1; Isononanoic acid (read-across)

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Acute Toxicity

<b>Test Substance</b>	Propanoic acid, 2,2-dimethyl-
<b>CAS No.</b>	75-98-9
<b>Method/Guideline</b>	Other
<b>Type of Study</b>	Acute oral toxicity
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Sprague-Dawley Rats
<b>Sex</b>	Males
<b>No. of animals/sex/dose</b>	5/dose
<b>Route of administration</b>	Gastric Intubation
<b>Vehicle</b>	None
<b>Frequency of Treatment</b>	Single Dose
<b>Dose/Concentration Levels</b>	34.6, 120, 417, 1450, 5000, and 10000 mg/kg
<b>Control group and Treatment</b>	None
<b>Remarks on Test Conditions</b>	The animals were fasted for a period of three to four hours prior to treatment. The animals were observed for toxic effects and mortality at one, four and 24 hours; and once daily thereafter for 14 days. A necropsy was performed on any animal that died. All surviving animals were weighed, sacrificed and necropsied.
<b>Results</b>	LD <sub>50</sub> = 2000 mg/kg (CL: 830-4820 mg/kg) Number of animals dead per number tested: 34.6, 120 and 417 mg/kg: 0/5 1450 mg/kg: 2/5 5000 mg/kg: 5/5 10,000 mg/kg: 5/5
<b>Remarks</b>	There were no deaths and no findings at necropsy in animals treated with 34.6, 120 and 417 mg/kg. At the 1450 mg/kg level, 2 of 5 animals died by day 2 and the remaining animals survived until the end of the study. These animals showed depression, severe dyspnea, depressed reflexes, sprawling, and lack of coordination. All animals in the 5000 and 10,000 mg/kg dose groups died within 48 hours of treatment. Severe depression, dyspnea, and prostration preceded death in all of the animals that died. Necropsy findings in high dose animals indicated congestion of lungs, liver, kidneys, and adrenals.
<b>Conclusions</b>	Under conditions of this study, Propanoic acid, 2,2-dimethyl- acid has a low order of acute oral toxicity in rats.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	October, 2000

# Acute Toxicity

<b>Test Substance</b> <b>CAS No.</b>  <b>Method/Guideline</b> <b>Type of Study</b> <b>GLP</b> <b>Year</b> <b>Species/strain</b> <b>Sex</b> <b>No. of animals/sex/dose</b> <b>Route of administration</b> <b>Vehicle</b> <b>Frequency of Treatment</b> <b>Dose/Concentration Levels</b> <b>Control group and Treatment</b>	Propanoic acid, 2,2-dimethyl- 75-98-9  Other Acute dermal toxicity Pre-GLP 1964 Rabbits/Albino Males and Females 2/sex/dose Dermal None Single Dose 50, 200, 794, 3160 mg/kg None
<b>Remarks on Test Conditions</b>	Undiluted test sample was applied to clipped, intact abdominal skin under a dental dam binder. The trunk was subsequently wrapped with gauze and adhesive tape. Following a 24-hour exposure period, binders were removed and the abdominal area was sponged with corn oil to remove sample residue. Following exposure, animals were observed for mortality or toxic effects at 1, 4, and 24 hours, and once daily thereafter for a total of 14 days. A necropsy was performed on any animal that died during the study. At the end of the 14-day observation period, all surviving animals were weighed, sacrificed, and necropsied.
<b>Results</b>	LD50 = 3160 mg/kg
<b>Remarks</b>	<p>In the highest dose group, two deaths occurred at 24 and 48 hours after exposure to the test substance. Death was preceded by marked depression, severe, dyspnea, prostration, excessive urination, and coma. Necropsy revealed congestion of the lungs, adrenals, kidneys, and blanched areas on the liver and spleen. In addition, inflammation of the bladder and gastrointestinal tract were noted. In the 794 mg/kg group, three of the four animals exhibited slight depression, dyspnea, unsteady gait with slight sprawling of the limbs at 24 hours after exposure to the test substance. However, by the third day post-exposure, all of the animals appeared normal. At the termination of the study, necrotic tissue was seen in the abdominal skin at the site of application of the test substance. Otherwise, no gross pathology was observed. In animals exposed to 50 and 200 mg/kg of the test substance, no signs of systemic toxicity were observed. These animals exhibited normal weight gain, appearance, and behavior.</p> <p>Dermal irritation was noted at all dose levels and was characterized by slight, transient erythema, edema, atonia, and desquamation at the lowest level. There was a dose-dependent increase in the intensity and persistence with pronounced irritation at the highest dose levels characterized by blanching, eschar formation, and necrosis.</p>
<b>Conclusions</b>	Under conditions of this study, Propanoic acid, 2,2-dimethyl- has a low order of acute dermal toxicity in rabbits.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	January, 2001

Acute Toxicity

<b>Test Substance CAS No.</b>	Propanoic acid, 2,2-dimethyl- 75-98-9
<b>Method/Guideline</b>	Other
<b>Type of Study</b>	Acute inhalation toxicity
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Rats Wistar, Mice/Swiss albino
<b>Sex</b>	Males
<b>No. of animals/sex/dose</b>	10/species
<b>Route of administration</b>	Inhalation
<b>Vehicle</b>	Other
<b>Frequency of Treatment</b>	Single 6-hour exposure
<b>Dose/Concentration Levels</b>	Saturated vapors - the mean nominal concentration was 4.0 mg/L.
<b>Control group and Treatment</b>	A group of mice and rats that served as a common control for the substances tested in this study were sacrificed and examined grossly.
<b>Remarks on Test Conditions</b>	An atmosphere of saturated vapors was produced by forcing air through a bubbler system that contained the test substance. 29 ml of liquid was vaporized at a flow rate of 23 L/min. Animals were caged in wire mesh compartments within the exposure chamber. Animals were observed for mortality and toxic effects at 30-minute intervals during exposure and daily thereafter. The animals were observed for two weeks following exposure, at which point animals were sacrificed and necropsied. Any animals that died during the exposure or observation periods were necropsied.
<b>Results</b>	Mouse LC50 < 4.0 mg/L Rat > 4.0 mg/L
<b>Remarks</b>	No deaths occurred among any of the animals during the inhalation exposure. Hyperactivity followed by prostration was observed in mice. All 10 mice died within the 24 hours following exposure. Two rats died on the second and fifth days. Rats displayed piloerection, epistaxis, and dyspnea following exposure. Due to advanced autolysis, necropsy of the animals that died did not reveal any meaningful findings. Necropsy of the animals that survived until termination of the study did not reveal any significant gross pathology.
<b>Conclusions</b>	Propanoic acid, 2,2-dimethyl- has a moderate order of inhalation toxicity in rodents.
<b>Data Quality</b>	2 - Valid with restrictions - No vapor concentration verification (analytical)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	January, 2001

# Repeat Dose Toxicity

<b>Test Substance</b> <b>CAS No.</b>  <b>Method/Guideline</b> <b>Type of Study</b> <b>GLP</b> <b>Year</b> <b>Species/strain</b> <b>Sex</b> <b>No. of animals/sex/dose</b> <b>Route of administration</b> <b>Vehicle</b> <b>Frequency of Treatment</b> <b>Dose/Concentration Levels</b> <b>Control group and Treatment</b>  <b>Statistical method</b>  <b>Remarks on Test Conditions</b>	Propanoic acid, 2,2-dimethyl- 75-98-9  Other Repeat dermal application Pre-GLP 1964 Albino Rabbits Male 4/dose Dermal Isopropyl Alcohol (IPA) 10 applications with a two-day rest between the 5th and 6th applications. 30mg/kg and 300mg/kg weight/volume solution in isopropyl alcohol Isopropyl Alcohol (IPA) was administered to 8 animals at a level of 2.5 ml/kg body weight per application. Not reported  The test material was applied to clipped abdominal skin. A loose gauze binder or a collar was used to prevent ingestion of the test substance. Animals were housed individually and allowed free access to food and water. Each animal was weighed, sacrificed, and necropsied 24 hours after the final application of test material. At the beginning of the study and prior to the final application, the following clinical parameters were evaluated: total erythrocyte count, total and differential leukocyte count, hematocrit, and urinalysis. Histological analysis was performed on sections of liver and kidney. Sections of brain, thyroid, lungs, heart, liver, kidneys, adrenals, skin, and bone marrow were preserved for possible future analysis.  For systemic effects: NOAEL = 300 mg/kg Propanoic acid, 2,2-dimethyl- produced moderate to severe skin irritation.  The control animals exhibited normal appearance and behavior throughout the study with the exception of nasal discharge in one animal and diarrhea in another. Slight body weight loss was observed during the first week, but the animals regained the weight and most animals showed overall weight gains by the end of the study. No treatment-related effects were observed at gross necropsy. Repeat applications did not cause any histopathological alterations to the liver or kidney of the rabbits.  Control animals exhibited slight erythema throughout the study and slight atonia and desquamation following the fifth application. Animals that received the test substance exhibited normal appearance and behavior throughout the study. Animals in the low dose group showed a net body weight gain by the end of the study and animals in the high dose group showed a slight weight loss by the end of the study. Gross pathological findings revealed parasitic infection of the liver and pitted kidneys in one rabbit, congested lungs in another, and congestion in the pancreas and kidney of a third rabbit. Slight to moderate erythema was observed in the low dose animals. Animals in the high dose group displayed moderate erythema, moderate edema, and moderate to marked atonia and desquamation. Three of the animals in the high dose group had areas of necrosis that persisted through the study.
<b>Results</b>	
<b>Remarks</b>	

**Robust Summaries - NEOacids C5-C28**

<b>Conclusions</b>	Under the conditions of this study, Propanoic acid, 2,2-dimethyl- has a low order of systemic toxicity following repeated dermal exposure.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Hazleton Laboratories, Inc. (1964) "Repeated Dermal Application - Rabbits," Unpublished report.
<b>Date last changed</b>	January 2001

**Acute Toxicity**

<b>Test Substance CAS No.</b>	Carboxylic acid, C6-8 neo 95823-36-2
<b>Method/Guideline Type of Study GLP Year Species/strain Sex No. of animals/sex/dose Route of administration Vehicle Frequency of Treatment Dose/Concentration Levels (mg/kg Control group and Treatment</b>	Other Acute oral toxicity Pre-GLP 1964 Sprague-Dawley Rats Males 5/dose Gastric Intubation Corn oil for 34.6, 120, 417, 1450 mg/kg doses Single Dose 34.6 (1%v/v), 120(1%v/v), 417(10%v/v), 1450(10%v/v), 5000 (undiluted), and 10000 (undiluted) mg/kg None
<b>Remarks on Test Conditions</b>	The animals were fasted for a period of three to four hours prior to treatment. The animals were observed for toxic effects and mortality at one, four and 24 hours; and once daily thereafter for 14 days. Necropsy was performed on any animal that died. All surviving animals were weighed, sacrificed and necropsied.
<b>Results</b>	LD <sub>50</sub> = 1860 mg/kg (No CL - all or none response)
<b>Remarks</b>	There were no principal toxic effects at 34.6, 120 and 417 mg/kg. In addition there were no findings at necropsy in these animals. At 1450 mg/kg, although there were no findings at necropsy, clinical signs were observed after dosing which included depression, dyspnea and slight to marked ataxia. At the two highest dose levels, all animals were dead within 24 hours. Prior to death, animals exhibited marked depression, sprawling of the limbs and depressed reflexes. Congestion of the lungs, kidneys and adrenals were observed in these animals.
<b>Conclusions</b>	Under conditions of this study, Carboxylic acid, C6-8 neo acid has a low order of acute oral toxicity in rats.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	January, 2001

### Acute Toxicity

<b>Test Substance</b>	Carboxylic acid, C6-8 neo
<b>CAS No.</b>	95823-36-2
<b>Method/Guideline</b>	Other
<b>Type of Study</b>	Acute dermal toxicity
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Albino Rabbits
<b>Sex</b>	Males and Females
<b>No. of animals/sex/dose</b>	2/sex/dose
<b>Route of administration</b>	Dermal
<b>Vehicle</b>	None
<b>Frequency of Treatment</b>	Single Dose
<b>Dose/Concentration Levels</b>	50, 200, 794, 3160 mg/kg
<b>Control group and Treatment</b>	None
<b>Remarks on Test Conditions</b>	Undiluted test sample was applied to clipped, intact abdominal skin under a dental dam binder. The trunk was subsequently wrapped with gauze and adhesive tape. Following a 24-hour exposure period, binders were removed and the abdominal area was sponged with corn oil to remove sample residue. Following exposure, animals were observed for mortality or toxic effects at 1, 4, and 24 hours, and once daily thereafter for a total of 14 days. A necropsy was performed on any animal that died during the study. At the end of the 14-day observation period, all surviving animals were weighed, sacrificed, and necropsied.
<b>Results</b>	LD50 > 3160 mg/kg
<b>Remarks</b>	<p>One death occurred in the 200 mg/kg group at 48 hours post-exposure, but this was not considered to be treatment-related, since no deaths occurred in any of the other treatment groups. Upon necropsy, cecal obstruction and a large amount of fluid in the abdominal cavity were found. No signs of systemic toxicity were seen in any of the animals exposed to 50, 200, or 794 mg/kg. In the highest dose group, marked depression, dyspnea, ataxia, and sprawling of the limbs were observed 1 to 4 hours after application. However, the animals had completely recovered by 24 hours following exposure and exhibited normal appearance and behavior for the remainder of the 14-day post-exposure period. Necropsy revealed no significant signs of gross pathology in these animals.</p> <p>Dose-dependent dermal irritation occurred at all of the doses tested. This ranged from slight to moderate erythema, atonia, and desquamation at the lower dose levels to moderate erythema and edema with atonia and desquamation at the two higher dose levels.</p>
<b>Conclusions</b>	Under conditions of this study, Carboxylic acid, C6-8 neo acid has a low order of acute dermal toxicity in rabbits.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	January, 2001

### Acute Toxicity

<b>Test Substance</b>	Carboxylic acid, C6-8 neo
<b>CAS No.</b>	95823-36-2
<b>Method/Guideline</b>	NA
<b>Type of Study</b>	Acute inhalation toxicity
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Rats/Albino, Mice/Albino
<b>Sex</b>	Males
<b>No. of animals/sex/dose</b>	10/species
<b>Route of administration</b>	Inhalation
<b>Vehicle</b>	None
<b>Frequency of Treatment</b>	Single 6-hour exposure
<b>Dose/Concentration Levels</b>	Saturated vapors - the mean nominal concentration was 3.0 mg/L.
<b>Control group and Treatment</b>	Groups of mice and rats that served as common controls for the substances tested in this study were sacrificed and examined grossly.
<b>Remarks on Test Conditions</b>	An atmosphere of saturated vapors was produced by forcing air through a bubbler system that contained the test substance. 31 ml of liquid was vaporized at a flow rate of 27 L/min. Animals were caged in wire mesh compartments within the exposure chamber. Animals were observed for mortality and toxic effects at 30-minute intervals during exposure and daily thereafter. The animals were observed for two weeks following exposure, at which point animals were sacrificed and necropsied. Any animals that died during the exposure or observation periods were necropsied.
<b>Results</b>	LD50 > 3.0 mg/L
<b>Remarks</b>	No significant toxic signs were observed during the 6-hour exposure period. All mice and rats appeared normal up to 5 days following exposure, when the mice developed urticaria. No deaths occurred in mice or rats throughout the study and no significant observations were made at necropsy.
<b>Conclusions</b>	Under conditions of this study, Carboxylic acid, C6-8 neo has a low order of acute inhalation toxicity in mice and rats.
<b>Data Quality</b>	2 - Valid with restrictions - No vapor concentration verification (analytical)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	January, 2001

### Repeat Dose Toxicity

<b>Test Substance</b>	Carboxylic acid, C6-8 neo
<b>CAS No.</b>	95823-36-2
<b>Method/Guideline</b>	Other
<b>Type of Study</b>	Repeat dermal application
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Albino Rabbits
<b>Sex</b>	Male
<b>No. of animals/sex/dose</b>	4/dose
<b>Route of administration</b>	Dermal
<b>Vehicle</b>	None
<b>Frequency of Treatment</b>	10 applications with a two-day rest between the 5th and 6th applications.
<b>Dose/Concentration Levels</b>	55.4 mg/kg, 553.7 mg/kg
<b>Control group and Treatment</b>	Isopropyl Alcohol (IPA) was administered to 8 animals at a level of 2.5 ml/kg body weight per application.
<b>Statistical method</b>	Not reported
<b>Remarks on Test Conditions</b>	<p>The test material was applied to clipped abdominal skin. A loose gauze binder or a collar was used to prevent ingestion of the test substance. Animals were housed individually and allowed free access to food and water. Each animal was weighed, sacrificed, and necropsied 24 hours after the final application of test material. At the beginning of the study and prior to the final application, the following clinical parameters were evaluated: total erythrocyte count, total and differential leukocyte count, hematocrit, and urinalysis. Histological analysis was performed on sections of liver and kidney. Sections of brain, thyroid, lungs, heart, liver, kidneys, adrenals, skin, and bone marrow were preserved for possible future analysis.</p>
<b>Results</b>	<p>For systemic effects: NOAEL = 553.7 mg/kg  Carboxylic acid, C6-8 neo produced moderate to severe skin irritation.</p>
<b>Remarks</b>	<p>Animals in the low dose group showed normal appearance behavior throughout the study. With the exception of one animal that showed a slight weight loss, the animals in the low dose group showed an overall body weight gain. In the high dose group, 3 of the 4 animals displayed normal appearance and behavior and either maintained their weight or had a slight weight loss. From the fifth through the ninth application, the fourth animal had labored breathing, weight loss, and was found dead 24 hours after the final application. Upon necropsy, this animal had congested and emphysematous lungs in addition to hemorrhagic areas in the renal medulla. The death of this animal was deemed to be unrelated to the treatment. Gross pathology of the remaining animals of the high dose group did not reveal any abnormalities other than a slight parasitic infection in the liver of one of the rabbits. Repeat applications did not cause any histopathological alterations to the liver or kidney of the rabbits.</p> <p>In the low dose animals, slight erythema was observed during the first week, with slight to moderate atonia and desquamation that followed the third application and lasted through the study. At the highest dose, slight to moderate erythema was observed and slight to moderate edema was present from the second through the fifth applications. After the fourth application, moderate to marked atonia, desquamation, and slight fissuring was observed through the remainder of the study. All animals showed areas of necrosis at the application site and in two animals, the skin was hypersensitive to touch.</p>

**RODENT SUMMARIES - NEOACIDS C5-C28**

<b>Conclusions</b>	Under the conditions of this study, Carboxylic acid, C6-8 neo has a low order or systemic toxicity following repeated dermal exposure.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Hazleton Laboratories, Inc. (1964) "Repeated Dermal Application - Rabbits," Unpublished report.
<b>Date last changed</b>	January 2001

## Developmental Toxicity

<b>Test Substance CAS No.</b>	Carboxylic acid, C6-8 neo 95823-36-2
<b>Method</b>	OECD 414
<b>Type of Study</b>	Developmental toxicity
<b>GLP</b>	Yes
<b>Year</b>	1986
<b>Species/Strain</b>	Sprague-Dawley Rats
<b>Sex</b>	Pregnant Females
<b>Number/sex/dose</b>	22/dose
<b>Route of administration</b>	Oral gavage
<b>Exposure Period</b>	Days 6-15 of gestation
<b>Concentrations</b>	0, 50, 250, 600, or 800 mg/kg
<b>Controls</b>	Controls received 800 mg/kg of distilled water
<b>Statistical methods</b>	ANOVA, Kruskal-Wallis, Fisher's exact test
<b>Remarks on Test Conditions</b>	Test material was assumed to be 100% pure for purposes of dosing. Physical examinations were performed and body weight and food consumption were measured throughout gestation. Mated females were sacrificed on gestational day 20 and a gross necropsy was performed. Uteri and ovaries were weighed and corpora lutea were counted. The number of implantation sites, early and late resorptions, and live and dead fetuses were determined. Full term fetuses were examined for abnormalities, weight, and crown-rump distance. From each litter, the heads of half of the fetuses were preserved and examined, while the other half of the fetuses were examined for skeletal malformations and ossification variations.
<b><u>Results</u></b>	NOAEL fetal: 250 mg/kg NOAEL maternal: 250 mg/kg
<b>Remarks for Results</b>	<p><b>Maternal:</b> The high dose of 800 mg/kg produced morbidity and mortality in 4 of the 22 mated females. This group displayed lethargy, abnormal breathing, rales, and staining around the muzzle and anogenital areas. Animals in the 600 mg/kg group had a significant incidence of rales. In the high dose group, group mean maternal body weight gain (800 mg/kg: 306.1±26.3g vs. CON: 391.9±29.7g) and uterine weight at term (800 mg/kg: 17.6±18.3g vs. CON: 76±18g) were significantly reduced. In the 600 mg/kg group, there was a significant reduction in body weight gain during the intervals of gd6-9 and gd0-20, although there was no statistically significant difference in body weight at term. Maternal food consumption was significantly reduced during gestational intervals gd6-9 and gd9-12 for both the 600 and 800 mg/kg groups and during gd12-16 in the 800 mg/kg group.</p> <p><b>Fetus:</b> In the high dose group, there was a significant increase in early embryonic resorptions with a corresponding decrease in the mean number of live fetuses. The remaining fetuses in the high dose group had significantly reduced fetal body weight (800 mg/kg males: 2.52±0.48g, 800 mg/kg females: 2.33±0.39g; CON males: 3.49±0.33g, Con females: 3.33±0.34g) and crown-rump distance. Microphthalmia and anophthalmia were observed in 14% of the fetuses from the high dose group. In addition, fused cervical vertebrae and misaligned thoracic vertebra were observed in the high dose group. Significant incidences of hydrocephalus and structural malformation of thoracic ribs occurred in both the 600 and 800 mg/kg groups. The fraction of malformed fetuses/live fetuses was significantly increased in the 600 and 800 mg/kg groups. In the 250 mg/kg group, there was an increase in the fraction of implants affected, however, this was not significantly different from the control group.</p>

## RODENT SUMMARIES - NEOACIDS C5-C28

<b>Results, continued</b>	Visceral examination revealed that the incidence of renal/ureter variations was significantly increased in the high dose group. In addition, the high dose group showed an increased incidence of unossified structures of the cranium, sternum, vertebrae, pelvis, and hindpaw. In both the 600 and 800 mg/kg groups, there were increases in the incidences of incompletely ossified supraoccipital and cervical vertebrae.
<b>Conclusions</b>	Carboxylic acid, C6-8 neo is embryo-lethal and teratogenic in rats at doses that are maternally toxic. Under the conditions of this study, Carboxylic acid, C6-8 neo is not a selective developmental toxicant.
<b>Data Quality</b>	1 - Reliable without restrictions
<b>Reference</b>	Exxon Biomedical Sciences (1986) "Oral teratology study in rats," Unpublished study.
<b>Date last changed</b>	January, 2001

### Acute Toxicity

<b>Test Substance</b>	Neodecanoic acid
<b>CAS No.</b>	26896-20-8
<b>Method/Guideline</b>	Other
<b>Type of Study</b>	Acute oral toxicity
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Rats/Sprague-Dawley
<b>Sex</b>	Males
<b>No. of animals/sex/dose</b>	5/dose
<b>Route of administration</b>	Gastric Intubation
<b>Vehicle</b>	Corn oil for 34.6, 120, 417, 1450 mg/kg
<b>Frequency of Treatment</b>	Single Dose
<b>Dose/Concentration Levels (mg/kg)</b>	34.6 (1%v/v), 120(1%v/v), 417(10%v/v), 1450(10%v/v), 5000 (undiluted), and 10000 (undiluted) mg/kg
<b>Control group and Treatment</b>	None
<b>Remarks on Test Conditions</b>	Test material was assumed to be 100% pure for purposes of dosing. The animals were fasted for a period of three to four hours prior to treatment. The animals were observed for toxic effects and mortality at one, four and 24 hours; and once daily thereafter for 14 days. Necropsy was performed on any animal that died. All surviving animals were weighed, sacrificed and necropsied.
<b>Results</b>	LD50= 2000 mg/kg (CL: 670-5980 mg/kg)
<b>Remarks</b>	There were no principal toxic effects or necropsy findings for animals in the 34.6, 120 and 417 mg/kg treatment groups. At 1450 mg/kg, 1 animal died within 24 hours of exposure and one animal died each day thereafter until all 5 animals were dead by day 5 of the study. Prior to death, slight to marked CNS depression, dyspnea, and ataxia was observed. In addition, congestion of the lungs, kidneys and adrenals were observed at necropsy. In the 5,000 mg/kg dose group, 2/5 animals died by 4 hours and 5/5 animals were dead by 24 hours following exposure. In the highest dose group, 4/5 animals died by 4 hours and all animals were dead by 24 hours post-treatment. Animals in the 5,000 and 10,000 mg/kg groups appeared to have depression, dyspnea, ataxia and sprawling of the limbs. Also at these two dose levels, necropsy findings indicated congestion of the lungs, liver, spleen, kidneys and adrenals.
<b>Conclusions</b>	
<b>Data Quality</b>	Neodecanoic acid has a low order of acute oral toxicity in rodents.
<b>Reference</b>	2 - Valid with restrictions (Pre-GLP)
<b>Date last changed</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.  October, 2000

### Acute Toxicity

<b>Test Substance</b>	Neodecanoic acid
<b>CAS No.</b>	26896-20-8
<b>Method/Guideline</b>	NA
<b>Type of Study</b>	Acute dermal toxicity
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Albino Rabbits
<b>Sex</b>	Males and Females
<b>No. of animals/sex/dose</b>	4/dose
<b>Route of administration</b>	Dermal
<b>Vehicle</b>	None
<b>Frequency of Treatment</b>	Single Dose
<b>Dose/Concentration Levels</b>	50, 200, 794, 3160 mg/kg
<b>Control group and Treatment</b>	None
<b>Remarks on Test Conditions</b>	<p>Test material was assumed to be 100% pure for purposes of dosing. Undiluted test sample was applied to clipped, intact abdominal skin under a dental dam binder. The trunk was subsequently wrapped with gauze and adhesive tape. Following a 24-hour exposure period, binders were removed and the abdominal area was sponged with corn oil to remove sample residue. Following exposure, animals were observed for mortality or toxic effects at 1, 4, and 24 hours, and once daily thereafter for a total of 14 days. A necropsy was performed on any animal that died during the study. At the end of the 14-day observation period, all surviving animals were weighed, sacrificed, and necropsied.</p>
<b>Results</b>	LD50 > 3160 mg/kg
<b>Remarks</b>	<p>No deaths occurred with any of the doses tested. The animals appeared normal in appearance and behavior throughout the study. All of the animals exhibited a normal pattern of weight gain. No signs of gross pathology were observed at necropsy.</p> <p>No dermal irritation was observed at the 50 mg/kg dose level and minimal irritation characterized by slight erythema, atonia, and desquamation that subsided in 10 days was noted at the 200 mg/kg level. At the 794 and 3160 mg/kg levels, a dose-dependent increase in the degree of irritation was observed. This consisted of slight to moderate erythema, which subsided after the fourth and eighth days, and slight to moderate atonia and desquamation that diminished in severity through the 14-day period.</p>
<b>Conclusions</b>	Under conditions of this study, Neodecanoic acid has a low order of acute dermal toxicity in rabbits.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	January, 2001

### Acute Toxicity

<b>Test Substance</b>	Neodecanoic acid
<b>CAS No.</b>	26896-20-8
<b>Method/Guideline</b>	Other
<b>Type of Study</b>	Acute inhalation toxicity
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/strain</b>	Rats/Wistar, Mice/Swiss albino
<b>Sex</b>	Males
<b>No. of animals/sex/dose</b>	10/species
<b>Route of administration</b>	Inhalation
<b>Vehicle</b>	None
<b>Frequency of Treatment:</b>	Single 6-hour exposure
<b>Dose/Concentration Levels:</b>	Saturated vapors - the mean nominal concentration was 3.0 mg/L.
<b>Control group and Treatment:</b>	A group of mice and rats that served as a common control for the substances tested in this study were sacrificed and examined grossly.
<b>Remarks on Test Conditions</b>	Test material was assumed to be 100% pure for purposes of dosing. An atmosphere of saturated vapors was produced by forcing air through a bubbler system that contained the test substance. 20 ml of liquid was vaporized at a flow rate of 21 L/min. Animals were caged in wire mesh compartments within the exposure chamber. Animals were observed for mortality and toxic effects at 30-minute intervals during exposure and daily thereafter. The animals were observed for two weeks following exposure, at which point animals were sacrificed and necropsied. Any animals that died during the exposure or observation periods were also necropsied.
<b>Results</b>	LD50 > 3.0 mg/L
<b>Remarks</b>	No mortality or significant signs of toxicity were observed during the 6-hour exposure period. No deaths occurred in mice or rats throughout the study and no significant observations were made at necropsy.
<b>Conclusions</b>	Under conditions of this study, Neodecanoic acid has a low order of acute inhalation toxicity in mice and rats.
<b>Data Quality</b>	2 - Valid with restrictions - No vapor concentration verification (analytical)
<b>Reference</b>	Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
<b>Date last changed</b>	January, 2001

**Acute Toxicity**

<p><b>Test Substance</b> <b>CAS No.</b></p> <p><b>Method/Guideline</b> <b>Type of Study</b> <b>GLP</b> <b>Year</b> <b>Species/strain</b> <b>Sex</b> <b>No. of animals/sex/dose</b> <b>Route of administration</b> <b>Vehicle</b> <b>Frequency of Treatment</b> <b>Dose/Concentration Levels</b> <b>Control group and Treatment</b></p>	<p>Neodecanoic acid 26896-20-8</p> <p>Other Acute inhalation toxicity No 1982 Rats/Wistar, Mice/Swiss albino, Guinea Pigs/Harley Males and Females 10/sex/species Inhalation None Single 6-hour exposure Liquid aerosol with a mean analytical concentration of 511 mg/m<sup>3</sup> 10/sex/species</p>
<p><b>Remarks on Test Conditions</b></p>	<p>Test material was assumed to be 100% pure for purposes of dosing. Groups of animals (10/sex/species) were exposed to either air only or to aerosolized test material. Aerosol was generated by pumping the test material into an atomizer at 15.0 psi. The resulting aerosol was sprayed into a glass aerosol diffuser, where it was mixed with incoming room air before entering the chamber. Exposure concentrations were determined on both a nominal and actual (gravimetric) basis. Particle size determinations were conducted twice during exposure. During the exposure, control and treated animals were observed every 15 minutes for the first hour and hourly thereafter. On the first day post-exposure, one half of the animals from each group were randomly selected and sacrificed, and an interim necropsy was performed. The remaining animals were observed daily for signs of toxicity for 14 days post-exposure. Body weights were recorded at the beginning of the study, and at 1, 2, 3, 4, 7, and 14 days post-exposure. A necropsy was performed on all animals that died or were sacrificed during the study. Major organs were examined for macroscopic abnormalities and lungs plus trachea, liver, kidneys, whole head, and any abnormal tissues were preserved. Organ weights were recorded at necropsy for lungs plus trachea, liver, and kidneys.</p>
<p><b>Results</b></p>	<p>LD50 &gt; 511 mg/m<sup>3</sup>; Mean Particle size: 2.99±1.76µm</p>
<p><b>Remarks</b></p>	<p>No animals died during the study. The control animals appeared normal throughout the exposure. During the two-week post-exposure period, incidences of ungroomed appearance, soft stool, and anogenital staining were observed in some of the control animals. One female guinea pig in the control group died on the fifth day of the post-exposure observation period.</p> <p>Animals exposed to the test material exhibited some signs of labored breathing, salivation, and eye irritation during the exposure. Upon removal from the chamber, exposed mice and guinea pigs had material-covered fur and exposed rats had some red staining around the nasal area, anogenital staining, soft stool, salivation, and lacrimation. During the two-week post-exposure observation period, all guinea pigs appeared normal. However, some of the mice appeared ungroomed and some rats exhibited anogenital staining and soft stool. Throughout the study, body weights remained normal except for a slight weight loss on the first and second post-exposure days in both the control and treated groups (all species). However, there was no statistically significant difference between control and treated groups.</p>

## RODENT SUMMARIES - NEOACIDS C5-C28

<b>Results, continued</b>	At terminal sacrifice, male mice exposed to the aerosolized test substance exhibited a statistically significant decrease in the liver to body weight ratio versus control animals. No other statistically significant differences were observed for group mean organ weight to body weight ratios. Minor macroscopic abnormalities were observed in both control and treated groups at the interim and terminal necropsies, but were not considered to be related to exposure to the test substance.
<b>Conclusions</b>	Under conditions of this study, aerosolized Neodecanoic acid has a low order of acute inhalation toxicity in mice, rats, and guinea pigs.
<b>Data Quality</b>	1 - Valid without restrictions
<b>Reference</b>	Bio/dynamics, Inc. (1982) "Evaluation of the Acute inhalation Toxicity in Rats, Mice, and Guinea Pigs". Unpublished report.
<b>Date last changed</b>	January, 2001

Repeat Dose Toxicity

<b>Test Substance</b>	Neodecanoic acid
<b>CAS No.</b>	26896-20-8
<b>Method</b>	Other
<b>Type of Study</b>	Repeat dermal application
<b>GLP</b>	Pre-GLP
<b>Year</b>	1964
<b>Species/Strain</b>	Albino Rabbits
<b>Sex</b>	Male
<b>Number/sex/dose</b>	4/dose
<b>Route of administration</b>	Dermal
<b>Vehicle</b>	None
<b>Exposure Period</b>	10 applications with a two-day rest between the 5th and 6th applications.
<b>Concentrations</b>	0.4 g/kg and 2.28 g/kg
<b>Controls</b>	Isopropyl Alcohol (IPA) was administered to 8 animals at a level of 2.5 ml/kg body weight per application.
<b>Statistical method</b>	Not reported
<b>Remarks on Test Conditions</b>	<p>Test material was assumed to be 100% pure for purposes of dosing. The test material was applied to clipped abdominal skin. A loose gauze binder or a collar was used to prevent ingestion of the test substance. Animals were housed individually and allowed free access to food and water. Each animal was weighed, sacrificed, and necropsied 24 hours after the final application of test material. At the beginning of the study and prior to the final application, the following clinical parameters were evaluated: total erythrocyte count, total and differential leukocyte count, hematocrit, and urinalysis. Histological analysis was performed on sections of liver and kidney. Sections of brain, thyroid, lungs, heart, liver, kidneys, adrenals, skin, and bone marrow were preserved for possible future analysis.</p>
<b>Results</b>	<p>For systemic effects: NOAEL = 2.28 g/kg Neodecanoic acid produced moderate skin irritation.</p>
<b>Remarks for Results</b>	<p>Wheezing was noted in one animal of the low dose group. However, the rest of the animals appeared normal in behavior and appearance throughout the study. Animals in the low dose group showed overall body weight gain while animals in the high dose group had a slight reduction in weight at the end of the study. Necropsy revealed parasitic areas on the liver and/or mesentery of three animals, emphysema in three animals, and fluid in the cranial cavity and sinuses of one animal. These findings, however, did not correlate with the dose of test material received and were not attributed to exposure to the test substance. Animals in both the low and high dose groups displayed a decrease in terminal total leukocyte count. However, these values were within the normal limit value for rabbits. Repeat applications did not cause any histopathological alterations to the liver or kidney of the rabbits.</p> <p>Animals in the low dose group displayed slight erythema and moderate atonia and desquamation starting on the first or fourth application and persisting through the remainder of the study. All animals in the high dose group had moderate erythema, moderate to marked atonia and desquamation, and slight edema after the fifth application. After seven applications, slight fissures were observed in some of the animals and the exposed skin became hypersensitive to touch.</p>

# **KODUST Summaries - Neoacids C5-C28**

<b>Conclusions</b>	Under the conditions of this study, Neodecanoic acid has a low order of systemic toxicity following subchronic dermal exposure.
<b>Data Quality</b>	2 - Valid with restrictions (Pre-GLP)
<b>Reference</b>	Hazleton Laboratories, Inc. (1964) "Repeated Dermal Application - Rabbits," Unpublished report.
<b>Date last changed</b>	January 2001

# Reproductive Toxicity

<p><b>Test Substance</b> <b>CAS No.</b></p> <p><b>Method/Guideline</b> <b>Type of Study</b> <b>GLP</b> <b>Year</b> <b>Species/strain</b> <b>Sex</b> <b>No. of animals/sex/dose</b> <b>Route of administration</b> <b>Frequency of Treatment</b> <b>Dose/Concentration Levels</b> <b>Control group and Treatment</b> <b>Duration of Test</b> <b>Pre-mating Exposure Period</b></p> <p><b>Remarks on Test Conditions</b></p>	<p>Neodecanoic acid 26896-20-8</p> <p>Other Reproductive Toxicity Pre-GLP 1968 Rats/Sprague-Dawley Males and Females P<sub>1</sub>: 80 females and 40 males Dietary Continuous 0, 100, 500, 1500 ppm in diet (5, 25, and 75 mg/kg/day) Purina Lab Chow, 0 ppm of test substance 3 generations P1: 9 weeks for both males and females</p> <p>Test material was assumed to be 100% pure for purposes of dosing. Pre-mating Period: For each dose level, 10 males and 20 females comprised the P<sub>1</sub> generation. The parental generation animals were maintained in individual cages and fed the corresponding diet for 9 weeks prior to mating. Individual body weights, food consumption, and observations of the physical appearance and behavior of the animals were recorded initially, at 5 weeks, and 9 weeks (P<sub>1</sub>), or at 8 weeks, and 12 weeks (P<sub>2</sub>). The F2B weanlings (P3) were fed the appropriate diets for 9 weeks and the same observations were recorded at 0, 8, and 9 weeks of exposure.</p> <p>Reproduction Period: Following 9 weeks of exposure, two females and 1 male from each group were housed together and allowed a 3-week mating period, during which time, males were rotated among the females on a weekly basis. 24 hours following birth of the F1A generation, litters were arbitrarily reduced to a maximum of 8 pups (4/sex) to be nursed. The number of conceptions, litters, live births, stillbirths, the size of natural and nursing litters, deaths during the period of lactation, and number of pups weaned were all recorded. The weights of the pups by sex were recorded at 24 hours and at weaning and all pups were observed for gross signs of abnormalities. Following the 21-day nursing period, representative pups from each litter were sacrificed and gross necropsies were performed. The remaining pups were discarded.</p> <p>One week following the weaning of the F1A litters, the P1 parents were re-mated in the same fashion to produce the F1B pups. Following the 21-day nursing period, 20 female and 10 male weanlings from each of the test groups were randomly designated as the P2 generation. The remaining F1B pups were sacrificed and necropsied. The P2 generation was fed the appropriate diet until 100 days of age and then mated in the same fashion to produce the F2A and F2B litters. The same procedures were followed as during the first reproductive phase. After the second litter, F2B, 20 females and 10 males were selected at random to be the P3 generation. Following 9 weeks of dietary administration to this generation, the study was terminated and gross necropsies were performed. The following tissues were preserved: brain, pituitary, eye, thyroid, lung, heart, liver, spleen, kidney, adrenal, stomach, pancreas, small and large intestine, urinary bladder, gonad, bone, bone marrow, and trachea. Tissues from 5 females and 5 males of the control and high dose groups underwent histological examination. In addition, sections of thyroid, lung, liver, kidney, adrenal and trachea from 5 females and 5 males of the low level and intermediate level groups were examined microscopically.</p>
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# **RODENT SUMMARIES - NEOACIDS C3-C28**

<b>Results</b>	<p>NOAEL Parental: 1500 ppm  NOAEL F1 Offspring: 1500 ppm  NOAEL F2 Offspring: 1500 ppm</p>
<b>Remarks</b>	<p>For all of the concentrations tested, no adverse effects were observed on survival, appearance, behavior, body weight gain, and food consumption in either the parental generation or either the F1 or F2 generations. In addition, the reproductive performance of the parents was not affected. No treatment-related gross or microscopic pathological findings were observed at any of the dietary levels.</p> <p>All of the P1 and P2 animals survived the pre-mating periods and all of the P3 animals survived the 9-week post-weaning period of exposure. The body weight gain, food consumption, appearance, and behavior of the rats in these test groups were comparable with that of the control rats. In the F1A and F1B litters, litter size, pup body weights, appearance, and behavior were comparable between the treated groups and the control group. There were a variety of incidental findings in pups of the F1A and F1B litters, however, pups of these litters did not display any signs of treatment-related toxicity. At necropsy, there were no gross alterations that could be attributed to exposure to the test substance. The F2A and F2B litters, similar to the F1 litters had incidental findings, but did not show any treatment-related signs of toxicity, or effects on litter size, pup body weights, appearance, or behavior. Examination of the F2B weanling pups also (P3) did not reveal any treatment-related abnormalities.</p>
<b>Conclusions</b>	<p>Under the conditions of this study, dietary exposure to Neodecanoic acid has a low order of reproductive toxicity in rats.</p>
<b>Data Quality</b>	<p>2 - Valid with restrictions (Pre-GLP)</p>
<b>Reference</b>	<p>Hazleton Labs, Inc. (1968) "Modified Three-Generation Reproduction Study - Rats," Unpublished report.</p>
<b>Date last changed</b>	<p>January 2001</p>

### Developmental Toxicity

<b>Test Substance</b> <b>CAS No.</b>	Isooctanoic Acid 25103-52-0
<b>Method/Guideline</b>	Other
<b>Type of Study</b>	Developmental Toxicity
<b>GLP</b>	Yes
<b>Year</b>	1995
<b>Species/strain</b>	Rat/Sprague-Dawley
<b>Sex</b>	Female
<b>No. of animals/sex/dose</b>	25/dose
<b>Route of administration</b>	Oral gavage
<b>Vehicle:</b>	Corn oil
<b>Dose/Concentration Levels</b>	0, 50, 200, 400, 800, and 1000 mg/kg/day
<b>Control group and Treatment</b>	Vehicle control: corn oil
<b>Statistical methods</b>	Statistical evaluation of equality of means was done by appropriate one way analysis of variance. Also, a standard regression analysis for linear response in the dose groups was performed.
<b>Remarks on Test Conditions</b>	<p>Test material was assumed to be 100% pure for purposes of dosing. Males and females were housed together until confirmation of mating. The presence of a sperm plug was set as gestational day (GD) 0. Mated females were dosed once daily from GD 6-15. Dosing volumes were 5 ml/kg for all groups and were based on the most recent body weight. Clinical observations were made daily during gestation. Food consumption and body weight measurements were made on every three days through GD21. On GD21, animals were euthanized and cesarean sections were performed. Gross necropsies were performed, uterine weights with ovaries were measured, uterine contents were examined, and uterine implantation data were recorded. All live fetuses were weighed, examined externally to determine sex and for gross malformations.</p>
<b>Results</b>	<p>Maternal NOAEL = 400 mg/kg/day                      Fetal NOAEL = 800 mg/kg/day</p>
<b>Remarks</b>	<p>Maternal: There were no treatment-related deaths during the study. However, there were some deaths in the different dose groups that were attributed to intubation errors. Animals in the 800 and 1000 mg/kg/day groups displayed clinical signs that included rales, stool abnormalities, and anogenital/abdominal staining following dose initiation on GD6. Animals in the remaining dose groups were free of clinical signs for the entire gestation period. Overall, there were no statistically significant differences in mean body weight gain for the entire gestation interval or the entire gestation interval corrected for uterine weight between treated and control animals. However, in the 800 and 1000 mg/kg/day groups, there were statistically significant decreases in body weight gain early during gestation (GD 6-15). This correlated with decreased mean food consumption in these groups during this time frame. In the 400 mg/kg/day group, there was evidence of slight body weight gain suppression during the interval following dosing. However, these animals recovered quickly and in the absence of a consistent response, this finding was considered the result of slight dosing trauma. There were no significant findings at necropsy other than some trauma that was indicative of dosing errors.</p>

## Robust Summaries - Neoacids C5-C26

<b>Results, continued</b>	<p>Fetal: There were no statistically significant differences in reproductive parameters including: total live fetuses, sex ratio, mean number of resorptions, mean number of implantation sites, mean number of corpora lutea, mean fetuses per implantation site, mean resorptions per implantation site, % pre-implantation losses, % post-implantation loss, or mean total affected (resorptions + dead + malformed fetuses per litter) between treated and control animals. No external abnormalities were observed in any fetuses from the control or treated groups. In the highest dose group, a statistically significant decrease in mean male and female fetal body weights was observed compared with the controls.</p>
<b>Conclusions</b>	<p>Under the conditions of this study, Isooctanoic acid is not a selective developmental toxicant.</p>
<b>Data Quality</b>	<p>2- reliable with restrictions - range-finding study.</p>
<b>Reference</b>	<p>Exxon Biomedical Sciences, Inc. (1995). "Developmental toxicity range-finding study in rats," Unpublished report.</p>
<b>Date last changed</b>	<p>October 22, 2001</p>

## Reproductive Toxicity

<b>Test Substance</b> <b>CAS No.</b>  <b>Method/Guideline</b> <b>Type of Study</b> <b>GLP</b> <b>Year</b> <b>Species/strain</b> <b>Sex</b> <b>No. of animals/sex/dose</b> <b>Route of administration</b> <b>Dose/Concentration Levels</b> <b>Control group and Treatment</b> <b>Statistics</b>	Isooctanoic Acid 25103-52-0  Other One-Generation Reproductive Toxicity Yes 1999 Rat/Sprague-Dawley Males and Females 10/sex/dose Dietary 0, 1000, 5000, 7500, and 10,000 ppm in diet 10/sex For the statistical analysis the percent of normal sperm were transformed by Bloom's transformation. All variables were analyzed by standard one-way analysis of variance (ANOVA). Residuals from the model were tested for normality by the Shapiro-Wilk. When there were differences in-group means based on the ANOVA, differences in means were tested using Duncan's multiple range test.
<b>Remarks on Test Conditions</b>	Test material was assumed to be 100% pure for purposes of dosing. P1 males and females (10 animals/sex) were exposed to the test substance for 10 weeks prior to mating. One male and one female were paired for up to 2 weeks. Beginning on GD 21, mated females were examined at least twice daily for signs of parturition. On PND 0, 1, 4, 7, 14 and 21 the offspring were counted, sexed and each live pup was weighed. Pups were counted and examined externally on a daily basis during the postnatal period. All animals were weighed and examined on PND 28, 35, 42, and 49 (males only were weighed and examined on PND Day 49). On PND 4, after counting, weighing, and examining the pups, the size of each litter was adjusted by eliminating extra pups by random selection to yield as nearly as possible, 4 males and 4 females per litter. Pups from each litter were examined daily for developmental landmarks. Sperm analyses were conducted at necropsy. Surviving F1 females were sacrificed on PND 42 and surviving F1 males were sacrificed on PND 49 unless they had not met criteria for vaginal patency or preputial separation, respectively.
<b>Results</b>	Maternal and Offspring NOAEL = 7500 ppm
<b>Remarks</b>	There were signs of a slight palatability problem with the 7500 ppm and 10,000 ppm diets with the males and the 10,000 ppm diet with the females as indicated by decreases in mean food consumption during the early part of the first week of the study. This problem resolved itself by the second week of the study. However, during the first week of gestation and for the entire postpartum period, mean food consumption was significantly decreased in the 10,000 ppm group females. There were no treatment-related clinical in-life observations, gross postmortem observations, or organ weight effect in the parental animals during this study. In addition, there were no statistically significant effects on reproductive indices or sperm parameters. The offspring displayed no treatment-related effects on survival, clinical observations, time to developmental landmarks, or offspring postmortem observations. Statistically significant suppression of body weight gain was observed in the 10,000 ppm adult females on PPD 4 and 14 when compared with controls. There were statistically significant decreases in the 10,000 ppm group's male mean offspring body weights on PND 14, 21, and 28. There also was a statistically significant decrease in the 10,000 ppm females' mean offspring body weight on PND 14 and 28. These decreases in body weight in dams and offspring were transient and were thought to be related to decreased maternal food consumption.

## Robust Summaries - Neoacids C5-C28

<b>Conclusions</b>	Under the conditions of this study Isooctanoic acid did not adversely affect reproductive parameters at doses that were nontoxic to the dams or their offspring.
<b>Data Quality</b>	1 - Reliable without restrictions
<b>Reference</b>	Exxon Biomedical Sciences, Inc. (1999) "One generation reproduction toxicity range-finding study in rats," Unpublished report.
<b>Date last changed</b>	August, 2001

### Reproductive Toxicity

<p><b>Test Substance</b> <b>CAS No.</b></p> <p><b>Method/Guideline</b> <b>Type of Study</b> <b>GLP</b> <b>Year</b> <b>Species/strain</b> <b>Sex</b> <b>No. of animals/sex/dose</b> <b>Route of administration</b> <b>Dose/Concentration Levels</b> <b>Control group and Treatment</b></p>	<p>Isononanoic Acid 3302-10-1</p> <p>Other One-Generation Reproductive Toxicity Yes 1998 Rat/Sprague-Dawley Males and Females 10/sex/dose Dietary 0, 600, 1200, 2500, 5000 ppm in diet 10/sex</p>
<p><b>Statistics</b></p>	<p>For the statistical analysis the percent of normal sperm were transformed by Bloom's transformation. All variables were analyzed by standard one-way analysis of variance (ANOVA). Residuals from the model were tested for normality by the Shapiro-Wilk. When there were differences in-group means based on the ANOVA, differences in means were tested using Duncan's multiple range test.</p>
<p><b>Remarks on Test Conditions</b></p>	<p>Test material was assumed to be 100% pure for purposes of dosing. P1 males and females (10 animals/sex) were exposed to the test substance for 10 weeks prior to mating. One male and one female were paired for up to 2 weeks. Beginning on GD 21, mated females were examined at least twice daily for signs of parturition. On PND 0, 1, 4, 7, 14, 21 and 28 the offspring were counted, sexed and each live pup was weighed. Pups were counted and examined externally on a daily basis during the postnatal period. On PND 4, after counting, weighing, and examining the pups, the size of each litter was adjusted by eliminating extra pups by random selection to yield as nearly as possible, 4 males and 4 females per litter. Pups from each litter were examined daily for developmental landmarks. Sperm analyses were conducted at necropsy. Surviving F1 females were sacrificed on PND 42 and surviving F1 males were sacrificed on PND 49 unless they had not met criteria for vaginal patency or preputial separation, respectively.</p>
<p><b>Results</b></p>	<p>Maternal and Offspring NOAEL = 1200 ppm</p>
<p><b>Remarks</b></p>	<p>There were no treatment-related deaths or clinical signs noted in the parental animals during this study. There also were no treatment-related clinical signs noted for the offspring. There were no treatment-related effects noted for the male reproductive parameters such as sperm motility, total cauda sperm count, homogenization resistant spermatid count, sperm morphology, or the reproduction indices of mean male fertility, male mating, female fertility, fecundity, or gestational indices. In addition, there were no treatment-related effects on absolute or relative reproductive organ weights.</p> <p>In the 5000 ppm dose group, statistically significant decreases in parental food consumption were attributed to reduced palatability of the diet. Decreases in body weights were noted in the 5000 ppm females at Gestation Days (GD) 7 and 21 and at Postpartum Days (PPD) 4, 7, and 14. Mean absolute and mean relative liver weights were increased in both sexes of the 5000 ppm group.</p> <p>The offspring of the 5000 ppm group had reduced Live Birth Index and reduced survival indices on Day 1 and Day 4. Also, offspring body weights of both sexes were reduced during the postnatal period. Offspring body weight was also reduced in males and female of the 2500 ppm group.</p>

# **KODUST Summaries - NEOACIDS C5-C28**

<b>Conclusions</b>	Under the conditions of this study the test substance did not adversely affect reproductive parameters at doses that were nontoxic to the dams or their offspring.
<b>Data Quality</b>	1 - Reliable without restrictions
<b>Reference</b>	Exxon Biomedical Sciences, Inc. (1998) "One generation reproduction toxicity range-finding study in rats," Unpublished report.
<b>Date last changed</b>	August, 2001

# 1. General Information

ID 7646-79-9

Date January 31, 2005

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## 1.0 SUBSTANCE INFORMATION

**Generic Name** : Cobalt chloride  
**Chemical Name** : Cobaltous chloride  
**CAS Registry No.** : 7646-79-9  
**Component CAS Nos.** :  
**EINECS No.** :  
**Structural Formula** :  $\text{CoCl}_2$   
**Molecular Weight** : 129.84  
**Synonyms and Tradenames** : Cobalt(II) chloride; Cobalt dichloride  
**References** : ATSDR, 2001. Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR), September 2001. (This reference is subsequently listed in this document as ATSDR Sept 2001 Draft).

## 2. Physico-Chemical Data

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### 2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	735 °C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Decomposes at 400 °C on long heating in air
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13 <sup>th</sup> Ed. Merck & Co., Inc., Whitehouse Station, NJ

### 2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	1,049 °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13 <sup>th</sup> Ed. Merck & Co., Inc., Whitehouse Station, NJ

### 2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	3.367 at 25 °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13 <sup>th</sup> Ed. Merck & Co., Inc., Whitehouse Station, NJ

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### 2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

### 2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Not applicable – metal dissociates (ionizes) in water
Reliability	:	
Reference	:	

### 2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	450 g/L at 7 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	544 g/L in ethanol; 86 g/L in acetone
Reliability	:	2 (reliable with restrictions): Source is well established data compendium
Reference	:	Weast. R.C. (ed.). 1988-1989. Handbook of Chemistry and Physics. 69 <sup>th</sup> Ed. CRC Press Inc., Boca Raton, FL., p. B-86.

## 2. Physico-Chemical Data

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### 2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

### 3. Environmental Fate & Transport

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#### 3.1.1 PHOTODEGRADATION

Type  
Guideline/method :  
Light source :  
Light spectrum :  
Relative intensity : based on  
Spectrum of substance : lambda (max, >295nm) :  
epsilon (max) :  
epsilon (295) :  
Conc. of substance : at °C  
DIRECT PHOTOLYSIS  
Halflife (t1/2) :  
Degradation : % after  
Quantum yield :  
INDIRECT PHOTOLYSIS  
Sensitizer :  
Conc. of sensitizer :  
Rate constant :  
Degradation :  
Deg. product :  
Year :  
GLP :  
Test substance :  
Deg. products CAS# :  
Method :  
Method detail :  
Result :  
Remark : Not applicable – metal does not degrade  
Reliability :  
Reference :

#### 3.2.1 MONITORING DATA

Type of measurement :  
Media :  
Concentration :  
Substance measured :  
Method :  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference :

#### 3.3.1 TRANSPORT (FUGACITY)

Type :  
Media :  
Air : % (Fugacity Model Level I)  
Water : % (Fugacity Model Level I)  
Soil : % (Fugacity Model Level I)  
Biota : % (Fugacity Model Level II/III)  
Soil : % (Fugacity Model Level II/III)  
Year :  
Test substance :  
Method :

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Method detail :  
Result :  
Remark :  
Reliability :  
Reference :

#### 3.5 BIODEGRADATION

Type :  
Guideline/method :  
Inoculum :  
Concentration : related to  
related to  
Contact time :  
Degradation : (±) % after day(s)  
Result :  
Kinetic of test subst. : % (specify time and % degradation)  
%  
%  
%  
%  
%  
Control substance :  
Kinetic : %  
%  
Deg. product :  
Year :  
GLP :  
Test substance :  
Deg. products CAS# :  
Method :  
Method detail :  
Result :  
Remark : Not applicable – the metal will not degrade  
Reliability :  
Reference :

#### 3.7 BIOCONCENTRATION

Type :  
Guideline/method :  
Species :  
Exposure period : at °C  
Concentration :  
BCF :  
Elimination :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference :

## 4. Ecotoxicity

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### 4.1 ACUTE TOXICITY TO FISH

Type	: Acute
Guideline/method	: Flow-through, freshwater
Species	: Rainbow trout ( <i>Onchorhynchus mykiss</i> )
Exposure period	: 96 hr
NOEC	:
LC0	:
LC50	: 1.41 mg Co/L (95% C.I. = 0.57 – 3.47 mg Co/L)
LC100	:
Other	: LC20 = 0.53 mg Co/L (95% C.I. = 0.24 – 1.20 mg Co/L)
Other	: Incipient lethal level for 50% mortality (time independent) = 0.35 mg Co/L
Other	: 144-hr LC50 = 0.52 mg Co/L (95% C.I. = 0.29 – 0.95 mg Co/L)
Limit test	:
Analytical monitoring	: Yes (results based on measured concentrations)
Year	: 1998
GLP	: No
Test substance	: Cobalt chloride dihydrate ( $\text{CoCl}_2 \cdot 2\text{H}_2\text{O}$ )
Method	:
Method detail	: Tests were conducted with trout fry in water with an alkalinity and hardness of approximately 25 mg $\text{CaCO}_3/\text{L}$ . Exposure concentrations ranged from 0.125 to 2.0 mg Co/L. Exposures were continued for up to 14 days, with mortality assessed every 2 hr for the first 48 hr, and every 6 h thereafter.
Result	: The onset of mortality was slow (48 hr or greater), generally not reaching a plateau for 200 hr or more.
Remark	: Study data indicate that the rainbow trout is highly sensitive to the toxic effects of cobalt. For comparison, reported 96-h LC50 values for other fish species include 22.0 mg Co/L for the fathead minnow ( <i>Pimephales promelas</i> ), 333 mg Co/L for the carp ( <i>Cyprinus carpio</i> ), and 275 mg Co/L for the mummichog ( <i>Fundulus heteroclitus</i> ) (U.S. EPA, ECOTOX data base, 2003). Available data suggest that toxicity to fish is reduced with increasing hardness up to a hardness of approximately 400 mg $\text{CaCO}_3/\text{L}$ (Diamond, J. et al., 1992. Aquat. Toxicol., 22:163-180).
Reliability	: 2 (Reliable with restrictions): comparable to guideline study
Reference	: Marr, J.C.A., J.A. Hansen, J.S. Meyer, D. Cacula, T. Podrabsky, J. Lipton, and H.L. Bergman. 1998. Toxicity of cobalt and copper to rainbow trout: application of a mechanistic model for predicting survival. Aquat. Toxicol., 43(4):225-238.

### 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	: Acute
Guideline/method	: Static, freshwater
Species	: <i>Daphnia magna</i> (water flea)
Exposure period	: 48 hr
NOEC	:
EC0	:
EC50	: 1.52 mg Co/L (95% C.I. = 1.01 - 2.28 mg Co/L)
EC100	:
Other	: 24 hr LC50 = 2.11 mg Co/L (95% C.I. = 1.49 - 3.05 mg Co/L)
Other	:
Other	:
Limit test	:
Analytical monitoring	: No
Year	: 1987
GLP	: No

## 4. Ecotoxicity

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<b>Test substance</b>	: Cobalt chloride hexahydrate (CoCl <sub>2</sub> · 6H <sub>2</sub> O)
<b>Method</b>	: American Public Health Association (APHA), 1976, Standard Methods for the Examination of Water and Wastewater.
<b>Method detail</b>	: Tests were conducted in well water with a total hardness of 240 mg CaCO <sub>3</sub> /L and a total alkalinity of 400 mg CaCO <sub>3</sub> /L. Solutions were not renewed during the test. Daphnids were not fed during the test.
<b>Result</b>	:
<b>Remark</b>	: In an older study, the 48-hr LC50 for <i>Daphnia magna</i> has been reported as 5.5 mg Co/L (Cabejszek and Stasiak, 1960 as cited in the U.S. EPA ECOTOX database, 2003). The 48-hr LC50 for another daphnid, <i>Daphnia hyaline</i> , has been reported as 1.52 mg Co/L (Baudouin and Scoppa, 1974 as cited in the U.S. EPA ECOTOX database, 2003). Others have found 48-hr LC50 values for <i>Ceriodaphnia dubia</i> of 2.35, 4.60, and 4.20 mg Co/L for tests conducted with water hardness of 50, 200, and 400 mg CaCO <sub>3</sub> /L, respectively (Diamond, J. et al., 1992. Aquat. Toxicol., 22:163-180).
<b>Reliability</b>	: 2 (Reliable with restrictions): comparable to guideline study
<b>Reference</b>	: Khangarot, B.S., P.K. Ray, and H. Chandra. 1987. <i>Daphnia magna</i> as a model to assess heavy metal toxicity: comparative assessment with mouse system. Acta. Hydrochim. Hydrobiol., 15(4): 427-432.

### 4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

<b>Type</b>	: Algal growth assay
<b>Guideline/method</b>	: Static, freshwater
<b>Species</b>	: <i>Chlorella vulgaris</i> (green algae)
<b>Endpoint</b>	: Population growth
<b>Exposure period</b>	: 96 hr
<b>NOEC</b>	:
<b>LOEC</b>	:
<b>EC0</b>	:
<b>EC10</b>	:
<b>EC50</b>	: 0.52 mg Co/L (95% C.I. = 0.48 – 0.56 mg Co/L)
<b>Other</b>	:
<b>Other</b>	:
<b>Other</b>	:
<b>Limit test</b>	:
<b>Analytical monitoring</b>	: No
<b>Year</b>	: 1993
<b>GLP</b>	:
<b>Test substance</b>	: Cobalt chloride
<b>Method</b>	:
<b>Method detail</b>	: Tests conducted in modified Bristol's medium (pH 6.5) with a 16:8 day/night photoperiod (280 foot candles). Cultures were incubated at 19°C ± 1°C. Results were based on experiments run in triplicate.
<b>Result</b>	: Growth was 63.8% and 28.4% of controls at concentrations of 0.32 and 1.00 mg Co/L, respectively.
<b>Remark</b>	: Other aquatic plants are much less sensitive to cobalt. The reported 96-h EC50 for <i>Spirulina platensis</i> (blue-green algae) is 23.8 mg Co/L (Sharma et al., 1987 as cited in the U.S. EPA ECOTOX database, 2003). The 7-d IC50 for <i>Lemna minor</i> (duckweed) is 16.9 mg Co/L (Dirilgen and Inel, 1994 as cited in the U.S. EPA ECOTOX database, 2003).
<b>Reliability</b>	: 2 (reliable with restrictions); comparable to guideline study
<b>Reference</b>	: Rachlin, J.W. and A. Grosso. 1993. The growth response of the green alga <i>Chlorella vulgaris</i> to combined divalent cation exposure. Arch. Environ. Contam. Toxicol., 24: 16-20.

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### 5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1 <sup>st</sup> . 2 <sup>nd</sup> . 3 <sup>rd</sup> .
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal, with increasing solubility resulting in increasing absorption (ATSDR Sept 2001 Draft). Approximately 13-34% of cobalt chloride, a soluble form, is absorbed in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. 1999. Cobalt. Clin. Tox. 37:201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

#### 5.1.1 ACUTE ORAL TOXICITY

Type	:	Oral
Guideline/Method	:	Not specified
Species	:	Rat
Strain	:	Wistar
Sex	:	Male and female
Number of animals	:	5 per sex per dose level
Vehicle	:	Distilled water
Doses	:	50, 600, 720, 864, and 1137 mg/kg

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**LD50** : 766 mg/kg as compound (hexahydrate); 95% C.I. = 677 – 867 mg/kg  
190 mg/kg as cobalt

**Year** : 1982

**GLP** : No

**Test substance** : Cobalt(II) chloride hexahydrate ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ )

**Method** : Single dose administered by gastric incubation

**Method detail** : Mortality assessed after a 10-d observation period.

**Result** :

**Remark** : Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg  $\text{CoCl}_2/\text{kg}$  bw (equivalent to 19.8 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate is reported to be similar to that of the chloride with oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 46.7 to 61.2 mg Co/kg b.w.) (ATSDR Sept 2001 Draft). For the mouse, LD50 values are 89.3 and 123 mg/kg for cobalt chloride and cobalt sulfate, respectively, which are equivalent to 40.2 and 46.7 mg Co/kg b.w. when expressed as the metal only (ATSDR Sept 2001 Draft).

**Reliability** : 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.

**Reference** : Speijers, G.J.A., E.I. Krajnc, J.M. Berkvens, and M.J. van Logten. 1982. Acute oral toxicity of inorganic cobalt compounds in rats. Food Chem. Toxicol., 20:311-314.

### 5.1.2 ACUTE INHALATION TOXICITY

**Type** :

**Guideline/method** :

**Species** :

**Strain** :

**Sex** :

**Number of animals** :

**Vehicle** :

**Doses** :

**Exposure time** :

**LC50** :

**Year** :

**GLP** :

**Test substance** :

**Method** :

**Method detail** :

**Result** :

**Remark** : No acute toxicity studies have been located for this compound.

**Reliability** :

**Reference** :

### 5.1.3 ACUTE DERMAL TOXICITY

**Type** :

**Guideline/method** :

**Species** :

**Strain** :

**Sex** :

**Number of animals** :

**Vehicle** :

**Doses** :

**LD50** :

**Year** :

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GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Increased proliferation of lymphatic cells was seen in rats, mice and guinea pigs dermally exposed to cobalt chloride in DMSO once per day for 3 consecutive days, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day (Ikarashi, Y., et al., 1992. Toxicology, 76:283-292). Stimulation indices of 3 or greater (indicative of a significant response by the authors), were reported for mice exposed to 1, 2.5 or 5% CoCl <sub>2</sub> (equivalent to 10.8, 27, or 54.1 mg Co/kg/day), rats exposed to 2.5 or 5% CoCl <sub>2</sub> (equivalent to 9.6 or 19.2 mg Co/kg/day), and guinea pigs exposed to 5% CoCl <sub>2</sub> (equivalent to 14.7 mg Co/kg/day).
Reliability	:	
Reference	:	

### 5.2.1 SKIN IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Dermatitis is a common result of dermal exposure to cobalt in humans and has been verified in a large number of studies (ATSDR Sept 2001 Draft). The dermatitis is probably caused by an allergic reaction to cobalt.
Reliability	:	
Reference	:	

### 5.2.2 EYE IRRITATION

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Concentration	:
Dose	:
Exposure time	:
Number of animals	:
Vehicle	:
Classification	:
Year	:
GLP	:

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Test substance :  
Method :  
Method detail :  
Result :  
Remark :  
Reliability :  
Reference :

### 5.4 REPEATED DOSE TOXICITY

Type : Repeated dose  
Guideline/method : Oral  
Species : Rat  
Strain : Not specified  
Sex : Male  
Number of animals : 30  
Route of admin. : Oral via stomach tube  
Exposure period : 150 to 210 days  
Frequency of treatment : Five days per week  
Post exposure period : 0 to 30 days  
Doses : 4 or 10 mg Co/kg  
Control group : Yes  
NOAEL :  
LOAEL : 4 mg Co/kg (organ weights increased)  
Other :  
Year : 1959  
GLP : No  
Test substance : Cobalt chloride  
Method :  
Method detail : The erythrocyte count, hemoglobin and hematocrit determinations were performed at frequent intervals for animals receiving 10 mg Co/kg. At study termination, all rats were sacrificed, organs examined and weighed, and sections made histological examination.

Result : The average weights of kidneys, livers, and spleens of the cobalt-treated groups were slightly heavier than the controls. Cobalt exposure at 10 mg/kg produced significant polycythemia. Histological examination of the kidneys revealed necrosis of the linings of the tubules in rats treated with 10 mg Co/kg, but not in those of the 4 mg Co/kg group. The effects was reversible, however, as examination of kidneys of rats autopsied 30 days after cobalt administration was discontinued showed no necrosis and were normal compared to the kidneys from control rats.

Remark : Results are highly consistent with those reported by others. Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and red blood cells; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).

Reliability : 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.

Reference : Murdock, H.R. 1959. Studies on the pharmacology of cobalt chloride. J. Amer. Pharm. Assoc., 48:140-142.

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Type	: Repeated dose
Guideline/method	: Not specified
Species	: Rat
Strain	: Sprague-Dawley
Sex	: Male
Number of animals	: 4
Route of admin.	: Oral
Exposure period	: 8 weeks
Frequency of treatment	: Daily
Post exposure period	: None
Doses	: 2.5, 10, or 40 mg/kg (equivalent to 0.6, 2.5, or 10 mg Co/kg)
Control group	: Yes
NOAEL	: 0.6 mg Co/kg
LOAEL	: 2.5 mg Co/kg (hemoglobin, red blood cell count)
Other	:
Year	: 1947
GLP	: No
Test substance	: Cobalt chloride hexahydrate ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ )
Method	:
Method detail	: Cobalt was administered orally in a gelatin capsule (mixed in equal part of wheat flour and powdered sugar). Blood counts and hemoglobin determinations were made at the start of the test and at two week intervals.
Result	: Hemoglobin content and numbers of erythrocytes were increased in rats receiving either 2.5 or 10 mg Co/kg/day, but not in those receiving 0.6 mg Co/kg/day.
Remarks	: Other researchers have reported similar results in long-term studies with rats although many study details are lacking in the published report (Krasovskii, G.N. and S.A. Fridlyand. 1971. Hyg. Sanit., 26:277-279). They found that oral doses of 0.5 and 2.5 mg Co/kg six days per week for seven months stimulated hemopoiesis and decreased immunological reactivity (reduced the phagocytic index). Daily doses of 0.5 mg Co/kg and greater also produced mild to moderate increases in conditioned flexes. However, daily doses of 0.05 mg Co/kg had no effects on the indices investigated. Others have also reported the neurotoxic and behavior effects of cobalt on rats after chronic dietary exposures (Nation, J.R. et al., 1983. Neurobehav. Toxicol. Teratol., 5:9-15).
Reliability	: 2 (reliable with restrictions): Documentation was incomplete; however, the results are highly consistent with others in the scientific literature.
Reference	: Stanley, A.J., H.C. Hopps, and A.M. Shideler. 1947. Cobalt polycythemia. II. Relative effects of oral and subcutaneous administration of cobaltous chloride. Proc. Soc. Exp. Biol. Med., 66:19-20.

### 5.5 GENETIC TOXICITY - MUTAGENICITY

Type	: Mutagenicity
Guideline/method	: Ames Assay
System of testing	: Bacteria <i>in vitro</i>
Species	: <i>Salmonella typhimurium</i> LT2
Strains	: TA100
Test concentrations	: $10^{-4}$ to $10^{-1}$ M
Cytotoxic concentr.	: $10^{-2}$ M
Metabolic activation	: No
Year	: 1981
GLP	: No
Test substance	: Cobalt chloride hexahydrate ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ )

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<b>Method</b>	: Ames, B.N., J. McCann, and E. Yamasaki. 1975. <i>Mutat. Res.</i> , 31:347-364.
<b>Method detail</b>	:
<b>Result</b>	: Negative both above and below the cytotoxic concentration
<b>Remark</b>	: Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt chloride, are generally nonmutagenic in <i>in vitro</i> bacterial assays (ATSDR Sept 2001 Draft). For example, cobalt chloride was not mutagenic in plate incorporation and fluctuation assays with <i>Salmonella</i> TA strains or a <i>Escherichia coli</i> WP2 strain (Arlauskas, A., et al., 1985. <i>Environ. Res.</i> , 36:379-388). However, a weak positive mutagenic response has been found in the rec assay with <i>Bacillus subtilis</i> at a concentration of 0.05 M (Kanematsu, N. et al., 1980. <i>Mutat. Res.</i> , 77:109-116). A very weak positive response has also been found in Chinese hamster V79 cells, but only at a highly cytotoxic concentration (Miyaki, M. et al. 1979. <i>Mutat. Res.</i> , 68: 259-263).
<b>Reliability</b>	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
<b>Reference</b>	: Tso, W-W. and W-P Fung. 1981. Mutagenicity of metallic cations. <i>Toxicolog. Lett.</i> , 8:195-200.
<b>Type</b>	: Mutagenicity
<b>Guideline/method</b>	: Ames Assay
<b>System of testing</b>	: Bacteria <i>in vitro</i>
<b>Species</b>	: <i>Salmonella typhimurium</i> LT2
<b>Strains</b>	: TA98, TA100, TA1537, and TA2637
<b>Test concentrations</b>	: 0.1 to 1,000 $\mu$ M/plate
<b>Cytotoxic conc.</b>	: Not specified
<b>Metabolic activation</b>	: No
<b>Year</b>	: 1986
<b>GLP</b>	: No
<b>Test substance</b>	: Cobalt chloride
<b>Method</b>	: Ames, B.N., J. McCann, and E. Yamasaki. 1975. <i>Mutat. Res.</i> , 31:347-364.
<b>Method detail</b>	: A modified Tris-HCl minimal medium with low phosphate content was used to prevent formation of insoluble metal phosphates in the test system.
<b>Result</b>	: Negative
<b>Remark</b>	: Although cobalt chloride alone did not produce mutants in this test system, it was mutagenic when it was added as a mixture with one of several heteroaromatic compounds (e.g., 4-aminoquinoline, 9-aminoacridine). The enhanced mutagenicity was attributed by the authors to the formation of weak to moderate complexes between these chemicals and the Co(II) cation, which may have enhanced transmembrane permeation or intercellular binding.
<b>Reliability</b>	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
<b>Reference</b>	: Ogawa, H.I., K. Sakata, T. Inouye, S. Jyosui, Y. Niyitani, K. Kamimoto, M. Morishita, S. Tsuruta, and Y. Kato. 1986. Combined mutagenicity of cobalt(II) salt and heteroaromatic compounds in <i>Salmonella typhimurium</i> . <i>Mutat. Res.</i> , 172: 97-104.

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### 5.6 GENETIC TOXICITY - CLASTOGENICITY

Type	: Chromosomal aberrations in bone marrow cells
Guideline/method	: <i>In vivo</i>
Species	: Mouse ( <i>Mus musculus</i> )
Strain	: Swiss albino
Sex	: Male
Route of admin.	: Oral (single dose)
Exposure period	: 6, 12, 18, or 24 hr.
Dose	: 20, 40 , or 80 mg/kg b.w.
Year	: 1991
GLP	: No
Test substance	: Cobalt chloride hexahydrate ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ )
Method	: Preston, R.J. et al., 1987. <i>Mutat. Res.</i> , 189:157.
Method detail	: Test compound was administered orally to five animals per dose group. Mice were 6-8 weeks old at that time. Colchicine (0.04%) was injected i.p. at 90 min prior to sacrifice. Bone marrow cells were removed from femurs by flushing with 0.8% sodium citrate. From each animal, 50 well-scattered metaphase plate were scored for chromosomal aberrations. Abnormalities were scored separately as total aberrations (with and without gaps) and as breaks per cell.
Result	: Administration of cobalt chloride produced a concentration-dependent increase in total chromosomal aberrations.
Remark	: Cobalt compounds, including soluble salts, are observed to be clastogenic (cause chromosomal aberrations) in a range of mammalian assay systems. For example, increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL) (ATSDR Sept 2001 Draft). There is evidence that soluble cobalt(II) cations exert a genotoxic activity in vitro and in vivo in experimental systems, but evidence in humans is lacking (Lison, D. et al., 2001. <i>Occup. Environ. Med.</i> , 58: 619-625).
Reliability	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	: Palit, S., A. Sharma, and G. Talukder. 1991. Chromosomal aberrations induced by cobaltous chloride in mice in vivo. <i>Biol. Trace Elem. Res.</i> , 29:139-145.
Type	: Micronucleus Test
Guideline/method	: <i>In vivo</i>
Species	: Mouse
Strain	: BALB/c AnNCrj
Sex	: Male
Route of admin.	: Intraperitoneally
Exposure period	: 30 hr
Doses	: 25, 50, or 90 mg Co/kg b.w.
Year	: 1993
GLP	: No
Test substance	: Cobalt chloride hexahydrate ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ )
Method	: Von Ledbur, M. and W. Schmid. 1973. <i>Mutat. Res.</i> , 19:109-117.
Method detail	: Mice were injected once ip and sacrificed after 30 hr. Bone marrow smears were prepared and stained. The incidence of micronucleated polychromatic erythrocytes (MPCE) was determined in 1,000 cells. In addition, the ratio of polychromatic erythrocytes (P) to normochromatic erythrocytes (N) was determined in 2,000 erythrocytes.
Result	: Treatment with cobalt induced a dose-dependent increase in the frequency of MPCE. The P/N ratio was significantly reduced ( $P < 0.05$ ) in mice dosed at 90 mg/kg b.w.

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<b>Remark</b>	: This study also included an <i>in vitro</i> micronucleus test with mouse bone marrow cells, both with and without metabolic activation with an S9 fraction. In contrast to the <i>in vivo</i> test, the <i>in vitro</i> test did not produce any significant changes in frequency of MPCE or the P/N ratio at dose levels of cobalt chloride hexahydrate up to 50 mg/L in the cell suspension.
<b>Reliability</b>	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
<b>Reference</b>	: Suzuki, Y., H. Shimizu, Y. Nagae, M. Fukumoto, H. Okonogi, and M. Kadokura. 1993. Micronucleus test and erythropoiesis: effect of cobalt on the induction of micronuclei by mutagens. <i>Environ. Mol. Mutagen.</i> , 22:101-106.
<b>Type</b>	: DNA damage in isolated human lymphocytes
<b>Guideline/method</b>	: Alkaline Comet Assay ( <i>in vitro</i> )
<b>Species</b>	: Human
<b>Strain</b>	:
<b>Sex</b>	: Female
<b>Route of admin.</b>	: In vitro
<b>Exposure period</b>	: 15 min
<b>Doses</b>	: 0.3, 0.6, 1.2, 1.5, 2.0, 2.5, 3.0, and 6.0 mg Co/L
<b>Year</b>	: 1998
<b>GLP</b>	: No
<b>Test substance</b>	: Cobalt chloride hexahydrate (CoCl <sub>2</sub> · 6H <sub>2</sub> O)
<b>Method</b>	: The alkaline comet assay performed using a modification of the method of Singh et al. 1988. <i>Exp. Cell. Res.</i> , 175:184-191.
<b>Method detail</b>	: Tests were conducted on lymphocytes taken from two healthy female donors. Cells were for 15 min exposed after 24 of stimulation by phytohaemagglutinin. After treatment, the cells were centrifuged for 10 min at 400 g. The supernatant was removed and the cell pellet was resuspended and processed for the alkaline comet assay (single cell electrophoresis assay). Fifty or 100 randomly selected slides were analyzed, with tail length, tail DNA, and tail movement recorded.
<b>Result</b>	: There was considerable interexperimental and interdonor variability in data; however, at the highest dose level (6.0 mg Co/L) there was a statistically significant increase in tail movement in all experiments, indicating DNA damage (single strand breaks and alkali labile sites). Tail movement was also increased at lower doses, but did not show a clear dose-dependent trend.
<b>Remark</b>	: Using human lymphocytes and macrophages (P388D <sub>1</sub> cells), an increase in sister chromatid exchanges (SCE) after exposure to cobalt chloride at 10 <sup>-4</sup> to 10 <sup>-5</sup> M has been also demonstrated (Andersen, O. 1983. <i>Environ. Health Perspect.</i> , 47: 239-253). Others have also found that cobalt chloride increases DNA strand breaks in human diploid fibroblasts and Chinese hamster ovary cells after <i>in vitro</i> exposures, although only when determined by alkaline sediment sucrose velocity sedimentation and not when measured by nucleoid sedimentation or nick translation assays (Hamilton-Koch, W. et al., 1986. <i>Chem.-Biol. Interactions</i> , 59:17-28).
<b>Reliability</b>	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
<b>Reference</b>	: De Beck, M., D. Lison, and M. Kirsch-Volders. 1998. Evaluation of the <i>in vitro</i> direct and indirect genotoxic effects of cobalt compounds using the alkaline comet assay. Influence of interdonor and interexperimental variability. <i>Carcinogenesis</i> , 19:2021-2029.

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### 5.8.2 DEVELOPMENTAL TOXICITY

**Type** : Developmental toxicity  
**Guideline/method** : Not specified  
**Species** : Rat  
**Strain** : Wistar  
**Sex** : Female  
**Route of admin.** : Gastric intubation  
**Exposure period** : Gestation day 14 through 21 days of lactation  
**Frequency of treatment** : Daily  
**Duration of test** : Through lactation day 21  
**Doses** : 12, 24, and 48 mg/kg b.w. (equivalent to 5.4, 10.8, or 21.8 mg Co/kg b.w.)  
**Control group** : Yes  
**NOAEL maternal tox.** : Not determined (no maternal data reported)  
**NOAEL teratogen.** : Malformations not observed  
**Other** :  
**Other** :  
**Other** :  
**Year** : 1985  
**GLP** : No  
**Test substance** : Cobalt chloride  
**Method** :  
**Method detail** : Cobalt chloride was administered to three groups of 15 pregnant rats from gestation day 14 through the 21<sup>st</sup> day of lactation. Pups were weighed and examined for signs of toxicity on days 1, 4, and 21 of lactation, and were sacrificed on day 21. Macroscopic examinations were made of the heart, lungs, spleen, liver, and kidneys following sacrifice. Clinical chemistry parameters were also measured.

**Result** : There was significant mortality of pups in the highest dose group and fewer litters produced at all dose levels. In addition, pups showed stunted growth (weight and length) at all dose levels. Relative weights of the liver (males and females) and spleen (females only) were reduced by cobalt exposure, but did not show a dose-related trend. Blood analysis and clinical chemistry showed no treatment related differences. No external malformations were observed in pups. Data from previous studies by the authors suggests that the upper two doses levels were maternally toxic, therefore, the results observed may have been indirectly due, at least in part, to effects on the mothers, rather than direct effects on the fetuses.

**Remark** :  
**Reliability** : 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.

**Reference** : Domingo, J.L., J.L. Paternain, J.M. Llobet, and J. Corbella. 1985. Effects of cobalt on postnatal development and late gestation in rats upon oral administration. Rev. Esp. Fisiol., 41:293-298.

**Type** : Teratogenicity  
**Guideline/method** : Not specified  
**Species** : Rat  
**Strain** : Sprague-Dawley  
**Sex** : Female  
**Route of admin.** : Oral gavage  
**Exposure period** : Day 6 to 15 of gestation  
**Frequency of treatment** : Daily  
**Duration of test** : To day 20 of gestation  
**Doses** : 25, 50, or 100 mg/kg (equivalent to 6.2, 12.4, and 24.8 mg Co/kg b.w.)  
**Control group** : Yes

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<b>NOAEL maternal tox.</b>	: Not determined (effects on weight gain seen at lowest dose)
<b>NOAEL teratogen.</b>	: 24.8 mg Co/kg b.w.
<b>Other</b>	: NOAEL for maternal hematology was 12.4 mg Co/kg b.w.
<b>Other</b>	:
<b>Other</b>	:
<b>Year</b>	: 1998
<b>GLP</b>	:
<b>Test substance</b>	: Cobalt chloride hexahydrate (CoCl <sub>2</sub> · 6H <sub>2</sub> O)
<b>Method</b>	:
<b>Method detail</b>	: Pregnant females (20 per group) were dosed daily with cobalt chloride hexahydrate in distilled water during gestation days 6 to 15. Maternal body weights were recorded on days 0, 6, 9, 12, 16, and 19 of gestation. Individual food consumption was recorded for the following intervals: days 0-6, 6-9, 9-12, 12-16 and 16-19. Detailed physical examinations for signs of toxicity were performed at the same time that weights were recorded. On day 20 of gestation, dams were weighed, then sacrificed. Blood samples were collected for hematological analyses. After exsanguinations, the uterine horns were opened, examinations made and the following recorded: number of corpora lutea, total implantations, number of live and dead fetuses number of resorptions, average fetus body weight, number of stunted fetuses, fetal body length, and fetal tail length. Fetuses were also fixed, stained and examined for skeletal abnormalities.
<b>Result</b>	: Maternal effects included significant reductions in weight gain and food consumption, particularly at the 24.8 mg Co/kg dose level, although effects on weight gain were found at all dose levels. Hematological parameters (e.g., hematocrit, hemoglobin content) were significantly increased in the highest dose group. No treatment-related changes were observed in the number of corpora lutea, total implants, resorptions, number of live and dead fetuses per litter, fetal size parameters, or fetal sex distribution data. Increased incidences of stunted fetuses per litter (those under two-thirds of the average fetus body weight) were seen in the two highest dose groups; however, the increases were not statistically significant. Examination of fetuses for gross external abnormalities, skeletal malformations, and ossification variations produced negative findings, indicating that cobalt doses as high as 24.8 mg Co/kg do not produce teratogenicity or significant fetotoxicity in the rat.
<b>Remark</b>	: A lack of teratogenicity in the golden hamster has also been reported (Ferm, V.H. 1972. Adv. Teratol., 6:51-75.
<b>Reliability</b>	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
<b>Reference</b>	: Paternain, J.L., J.L. Domingo, and J. Corbella. 1988. Developmental toxicity of cobalt in the rat. J. Toxicol. Environ. Health, 24:193-200.
<b>Type</b>	: Developmental toxicity
<b>Guideline/method</b>	: Chernoff/Kavlock developmental toxicity screen
<b>Species</b>	: Mouse
<b>Strain</b>	: ICR/SIM
<b>Sex</b>	: Female
<b>Route of admin.</b>	: Oral intubation
<b>Exposure period</b>	: Gestation days 8 through 12
<b>Frequency of treatment</b>	: Daily
<b>Duration of test</b>	: Through postnatal day 3
<b>Dose</b>	: 180 mg/kg/day (equivalent to 81.7 mg Co/kg)
<b>Control group</b>	: Yes
<b>NOAEL maternal tox.</b>	: Not determined
<b>NOAEL teratogen.</b>	: 180 mg/kg/day (equivalent to 81.7 mg Co/kg)
<b>Other</b>	:

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Other	:	
Other	:	
Year	:	1986
GLP	:	
Test substance	:	Cobalt chloride
Method	:	Chernoff, N. and R.J. Kavlock. 1982. J. Toxicol. Environ. Health, 10:541-550.
Method detail	:	The screening test was carried out with a single minimally dose that was expected to result in significant maternal weight reduction, up to 10% mortality, or other clinical sings of overt toxicity. Treatment was by oral intubation on days 8 through 12 of gestation. Mice were allowed to deliver, and neonates examined, counted, and weighed on the day of birth (day 1) and day 3. Dead neonates were recovered from the nest and examined for abnormalities.
Result	:	The average maternal weight gain was significantly affected by cobalt treatment as desired in the protocol. Despite this, there was no effect of cobalt on litter size, percent survival of neonates on days 1-3, or average neonatal weight.
Remark	:	Results are in agreement with those seen in the rat, although another researcher has reported that injections of cobalt chloride to pregnant mice can lead to interference of skeletal ossification in fetuses (Wide, M. 1984. Environ. Res., 33:47-53).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Seidenberg, J.M. D.G. Anderson, and R.A. Becker. 1986. Validation of an in vivo developmental toxicity screen in the mouse. Teratog. Carcinog. Mutagen., 6:361-374.

### 5.8.3 TOXICITY TO REPRODUCTION

Type	:	Male reproduction
Guideline/method	:	Not specified
In vitro/in vivo	:	In vivo
Species	:	Mouse
Strain	:	CD-1
Sex	:	Male
Route of admin.	:	Drinking water
Exposure period	:	12 weeks (dose-response study); 13 weeks (time course study)
Frequency of treatment	:	Continuous
Duration of test	:	12 weeks (dose-response study); 33 weeks (time course study)
Doses	:	10, 200, or 400 ppm in the dose-response study (equivalent to a daily intake of 23.0, 42.0, or 72.1 mg Co/kg b.w.); 400 ppm in the time course study (equivalent to a daily intake of 58.9 mg Co/kg b.w.)
Control group	:	Yes
Year	:	1988
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate (CoCl <sub>2</sub> · 6H <sub>2</sub> O)
Method	:	
Method detail	:	In the dose-response study, males (5 per dose) were evaluated after 12 weeks of exposure for testicular weight, epididymal sperm concentration, sperm motility, sperm fertilizing ability (fertility), prostatic weight, seminal vesicle weight, and serum levels of testosterone. In the time course study, males (5 per dose and time point) were evaluated after 7, 9, 11, or 13 weeks of exposure for most of these same parameters. In addition, fertility of the males was evaluated at regular intervals up to 20 weeks after cessation of cobalt treatment in the drinking water.
Result	:	Cobalt exposure affected male reproductive parameters in a time- and

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	<p>dose-dependent manner. There was a significant decrease in testicular weight and epididymal sperm concentration after 11-13 weeks of exposure at all dose levels. Sperm motility and fertility were significantly depressed in the highest exposure groups. After cessation of exposure, some recovery was seen in fertility over time; however, indices remained significantly depressed through study termination (20 weeks after cessation). Parallel studies with acute cobalt chloride exposures (i.p injections of 200 <math>\mu</math>moles/kg for 3 consecutive days) did not result in significant changes in male reproductive parameters, although transient affects on fertility were observed.</p>
Remark	: Histopathology studies of testes from mice treated with the same general exposure regimen as in this study (i.e., 400 ppm in drinking water for 13 weeks) showed a reproducible, sequential pattern of seminiferous tubule degeneration (Anderson, M.B. et al., 1992. <i>Reprod. Toxicol.</i> , 6:41-50). Results of this study are highly consistent with others in which testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water (ATSDR Sept 2001 Draft).
Reliability	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	: Pedigo, N.G., W.J. George, and M.B. Anderson. 1988. Effects of acute and chronic exposure to cobalt on male reproduction in mice. <i>Reprod. Toxicol.</i> , 2:45-53.
Type	: Male reproduction
Guideline/method	: Not specified
In vitro/in vivo	: In vivo
Species	: Rat
Strain	: Sprague-Dawley
Sex	: Male
Route of admin.	: Diet
Exposure period	: 98 d
Frequency of treatment	: Continuous in diet
Duration of test	: Up to 98 d
Doses	: 265 ppm in diet (equivalent to 20 mg Co/kg b.w. at test initiation)
Control group	: Yes
Year	: 1985
GLP	: No
Test substance	: Cobalt chloride hexahydrate ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ )
Method	:
Method detail	: Three rats from the control and treatment groups were sacrificed on days 1, 2, 7, 14, 21, 28, 35, 42, 56, 63, 70, 84, and 98. Tissue specimens from the testes, cauda epididymus, and seminal vesicles were fixed and later examined.
Result	: Dietary cobalt exposure induced consistent degenerative and necrotic lesions in the seminiferous tubules of rats. Cyanosis and engorgement of testicular vasculature on day 35 and thereafter was followed on day 70 by degenerative and necrotic changes in the germinal epithelium and Sertoli cells. Findings indicate that cobalt readily crosses the blood-testes barrier.
Remark	: Results are consistent with those of Nation et al. (1983), who found significant testicular atrophy in rats exposed chronically to 20 mg Co/kg in the diet (Nation, J.R. et al., 1983. <i>Neurobehav. Toxicol. Teratol.</i> , 5:9-15).
Reliability	: 2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	: Corrier, D.E., H.H. Mollenhauer, D.E. Clark, M.F. Hare, and M.H. Elissalde. 1985. Testicular degeneration and necrosis induced by dietary cobalt. <i>Vet. Pathol.</i> , 22:610-616.

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### **6.0 OTHER INFORMATION**

#### **6.1 CARCINOGENICITY**

The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). "No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt." (ATSDR Sept 2001 Draft).

# 1. General Information

ID 136-52-7

Date November 7, 2005

201-16121B9

## 1.0 SUBSTANCE INFORMATION

**Generic Name** : Hexanoic acid, 2-ethyl, cobalt salt  
**Chemical Name** : Hexanoic acid, 2-ethyl, cobalt (2+) salt  
**CAS Registry No.** : 136-52-7  
**Component CAS Nos.** :  
**EINECS No.** :  
**Structural Formula** :  $C_{16}H_{30}CoO_4$   
**Molecular Weight** : 345.3438  
**Synonyms and Tradenames** : Cobalt 2-ethylhexanoate; Cobalt octoate  
**References** : <http://www.chemfinder.com>; MSDS prepared by The Shepherd Chemical Company, dated 3/26/02.

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## 2. Physico-Chemical Data

ID 136-52-7

Date November 7, 2005

### 2.1 MELTING POINT

Type	: Melting Point/Melting Range Determination
Guideline/method	: OECD 102; EPA OPPTS 830.7200
Value	: About 120°C
Decomposition	: At about 120°C
Sublimation	:
Year	: 2003
GLP	: Yes
Test substance	: Hexanoic acid, 2-ethyl, cobalt (2+) salt, Batch LB 1736-41, 17.0% cobalt, blue, semi-solid
Method	: OECD 102, Melting Point/Melting Range, July 1995; EPA Product Properties Test Guidelines, OPPTS 830.7200, Melting Point/Melting Range, March 1998
Method detail	: A differential scanning calorimeter (DSC 821, Fa, Mettler Toledo) was used to determine the melting point/range (the temperature or temperature range at which phase transition from solid to liquid state occurs). A preliminary test was conducted at a heating rate of 20 K/min from 25°C to 200°C and the quantities of heat absorbed or released were measured and recorded. The weight and appearance of the sample were recorded before and after the test. Based upon the preliminary test results, three definitive runs were made to determine the onset and end of the endothermic reaction. The first run was from 40°C - 95°C, the second run was from 40°C - 130°C, and the third run was from 90°C - 140°C.
Result	: The results indicate that the test substance most probably melted under decomposition at about 120°C.
Remark	: <b>Supporting data for dissociation products:</b> <b>Acid:</b> Melting point is reported as -118.4°C for 2-ethylhexanoic acid (Appendix B). <b>Metal:</b> The reported melting point for cobalt chloride is 735°C (Appendix G).
Reliability	: [1] Reliable without restriction
Reference	: Tognucci, A., 2003. Determination of the Melting Point/Melting Range of Hexanoic acid, 2-ethyl, cobalt (2+) salt, RCC Study No. 849070, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

### 2.2 BOILING POINT

Type	: Boiling Point/Boiling Range Determination
Guideline/method	: OECD 103; EPA OPPTS 830.7220
Value	: Could not be determined under conditions of the test
Decomposition	: At about 120°C
Year	: 2003
GLP	: GLP
Test substance	: Hexanoic acid, 2-ethyl, cobalt (2+) salt, Batch LB 1736-41, 17.0% cobalt, blue, semi-solid
Method	: OECD 103, Boiling Point, July 1995 (visual test with capillary tester); EPA Product Properties Test Guidelines, OPPTS 830.7220, Boiling Point/Boiling Range, August 1996
Method detail	: Ground test substance was packed into two small tubes and boiling capillaries inserted. Samples were heated from 25°C to 400°C in a BUECHI Melting Point Tester, B-545. The rate of heating was 20 K/min. Samples were observed visually through a lens for the presence of a stream of bubbles, indicative of boiling. The temperature at which this occurs is the boiling point.
Result	: Starting at about 300°C, the color of the samples became brighter and changed to blue. The boiling point or boiling range could not be determined.

## 2. Physico-Chemical Data

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**Remark** : **Supporting data for dissociation products:**  
**Acid:** Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (Appendix B).  
**Metal:** The reported boiling point for cobalt chloride is 1,049°C (Appendix G).

**Reliability** : [1] Reliable without restriction

**Reference** : Tognucci, A., 2003. Determination of the Boiling Point/Boiling Range of Hexanoic acid, 2-ethyl, cobalt (2+) salt, RCC Study No. 849071, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

### 2.3 DENSITY

**Type** :  
**Guideline/method** :  
**Value** :  
**Year** :  
**GLP** :  
**Test substance** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** : **Supporting data for dissociation products:**  
**Acid:** The reported density of 2-ethylhexanoic acid is 0.903 ([www.chemfinder.com](http://www.chemfinder.com)).  
**Metal:** The reported density of cobalt (II) chloride is 3.367 at 25°C (Appendix G).

**Reliability** :  
**Reference** :

### 2.4 VAPOR PRESSURE

**Type** :  
**Guideline/method** :  
**Value** :  
**Decomposition** :  
**Year** :  
**GLP** :  
**Test substance** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** : **Supporting data for dissociation products:**  
**Acid:** Vapor pressure is reported as  $1.33 \times 10^{-3}$  kPa at 20°C for 2-ethylhexanoic acid (Appendix B).

**Reliability** :  
**Reference** :

### 2.5 PARTITION COEFFICIENT

**Type** :  
**Guideline/method** :  
**Partition coefficient** :  
**Log Pow** :  
**pH value** :  
**Year** :  
**GLP** :  
**Test substance** :

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Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (Appendix B).  
**Metal:** not applicable. Cobaltous chloride dissociates in water.

Reliability :  
Reference :

### 2.6.1 SOLUBILITY IN WATER

Type : Water solubility determination  
Guideline/method : OECD 105; EPA OPPTS 830.7840  
Value : 28.8 mg/L at 20°C  
pH value :  
concentration : at °C  
Temperature effects :  
Examine different pol. :  
PKa : at °C  
Description :  
Stable :  
Deg. product :  
Year : 2004  
GLP : Yes  
Test substance : Hexanoic acid, 2-ethyl, cobalt (2+) salt, batch LB1736-41, 17% Co by weight, blue semi-solid

Deg. products CAS# :  
Method : OECD 105, Water Solubility, 1995; EPA Product Properties Test Guidelines, OPPTS 830.7840, Water Solubility: Column Elution Method, Shake Flask Method, 1998.

Method detail : A preliminary test indicated that the column elution method was appropriate. Glass beads (6.01 g) were weighed and placed in a 100 mL round bottom flask. Test item (0.126 g) and dichloromethane (10 mL) were added and the mixture sonicated. The dichloromethane was then evaporated using a gentle stream of nitrogen. The loaded carrier was poured into the elution column which was then filled with water. The system was equilibrated for approximately 2 hours. Elution of the test material from the carrier was performed using a circulation pump. Test temperature was 20°C. The flow rate was 0.52 mL/min in the first part of the test (about 51 hours) and 0.26 mL/min in the second part of the test (about 24 hours). The apparatus was run until equilibration of the saturation column was obtained, defined by at least five successive samples whose concentrations do not differ more than 30%. The column eluate was sampled at intervals of at least 1 hour to determine the concentration of cobalt, using atomic absorption spectroscopy.

Result : Based upon the results of 12 samples, the cobalt solubility was 4.9 mg/L (SD ± 0.1 mg/L) which corresponds to a water solubility of hexanoic acid, 2-ethyl, cobalt salt of 28.8 mg/L (calculated based on cobalt content of 17.0%).

Remark : **Supporting data for dissociation products:**  
**Acid:** The water solubility of 2-ethylhexanoic acid was reported to be 25 mg/L at 25°C (Appendix B).  
**Metal:** The water solubility of cobalt (II) chloride was reported to be 450 g/L at 7°C (Appendix G).

Reliability : [1] Reliable without restriction  
Reference : Tognucci, A., 2004. Determination of the water solubility of hexanoic acid,

## 2. Physico-Chemical Data

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2-ethyl, cobalt (2+) salt. RCC Study No. 849073, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

### 2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable
Year	:	
GLP	:	
Test substance	:	Cobalt 2-ethylhexanoate, blue semi-solid, 17% Co by weight
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> A flashpoint of 118°C was reported for 2-ethylhexanoic acid (Appendix B).
Reliability	:	
Reference	:	MSDS dated 3/26/02, prepared by The Shepherd Chemical Company

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#### 3.1.1 PHOTODEGRADATION

Type  
Guideline/method :  
Light source :  
Light spectrum :  
Relative intensity : based on  
Spectrum of substance : lambda (max, >295nm) :  
epsilon (max) :  
epsilon (295) :  
Conc. of substance : at °C  
**DIRECT PHOTOLYSIS**  
Half-life (t1/2) :  
Degradation : % after  
Quantum yield :  
**INDIRECT PHOTOLYSIS**  
Sensitizer :  
Conc. of sensitizer :  
Rate constant :  
Degradation :  
Deg. product :  
Year :  
GLP :  
Test substance :  
Deg. products CAS# :  
Method :  
Method detail :  
Result :  
Remark : **Supporting data for dissociation products:**  
**Acid:** 2-ethylhexanoic acid is predicted to undergo direct hydrolysis with a half-life of 16 hours, according to AOP v.191 in the EPIWIN v.3.11 program (Appendix B).  
**Metal:** Photodegradation is not applicable for cobalt chloride.  
Reliability :  
Reference :

#### 3.1.2 DISSOCIATION

Type : Dissociation constant determination  
Guideline/method : OECD 112  
pKa : 6.41 at 20°C  
Year : 2002  
GLP : Yes  
Test substance : Cobalt (II) 2-ethylhexanoate, lot number LB1736-40, received from Shepherd Chemical Company. Blue solid, purity of 17.0% cobalt.  
Approximate water solubility : 50 mg/L as determined visually in preliminary study  
Method : OECD Guideline 112, Dissociation Constants in Water  
Method detail : Three replicate samples of cobalt (II) 2-ethylhexanoate were prepared at a nominal concentration of 25 mg/L by fortification of 100 mL degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.002 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the first equivalence point (with one exception) and the titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 10 points (with one exception) on the

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titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

**Result** : Mean (N = 3) pKa value was 6.41 (SD = 0.0645) at 20°C

**Remark** : The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

**Reliability** : [1] Reliable without restriction.

**Reference** : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of cobalt (II) 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-105, conducted for the Metal Carboxylates Coalition.

#### 3.2.1 MONITORING DATA

**Type of measurement** :  
**Media** :  
**Concentration** :  
**Substance measured** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** :  
**Reliability** :  
**Reference** :

#### 3.3.1 TRANSPORT (FUGACITY)

**Type** :  
**Media** :  
**Air** : % (Fugacity Model Level I)  
**Water** : % (Fugacity Model Level I)  
**Soil** : % (Fugacity Model Level I)  
**Biota** : % (Fugacity Model Level II/III)  
**Soil** : % (Fugacity Model Level II/III)  
**Year** :  
**Test substance** :  
**Method** :  
**Method detail** :  
**Result** :  
**Remark** :

##### Supporting data for dissociation products:

**Acid:** Assuming equal distribution to all compartments, the Level III Fugacity Model (EPIWIN v3.11) predicts distribution of 2-ethylhexanoic acid as follows: 5.29% to air, 41.6% to water, 53% to soil, and 0.197% to sediment. The predicted persistence time is 190 hours (Appendix B).

**Reliability** :  
**Reference** :

#### 3.5 BIODEGRADATION

**Type** :  
**Guideline/method** :  
**Inoculum** :  
**Concentration** : related to  
related to  
**Contact time** :  
**Degradation** : (±) % after day(s)  
**Result** :

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Kinetic of test subst. : % (specify time and % degradation)

:  
%  
%  
%  
%

Control substance :

Kinetic : %  
%

Deg. product :

Year :

GLP :

Test substance :

Deg. products CAS# :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**

**Acid:** Aerobic biodegradation of 2-ethylhexanoic acid was reported from a study with non-acclimated activated sludge, similar to OECD Guideline 301D. The resulting BOD<sub>5</sub>, BOD<sub>10</sub> and BOD<sub>20</sub>, respectively, was 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (Appendix B).

**Metal:** metal does not degrade.

Reliability :

Reference :

#### 3.7 BIOCONCENTRATION

Type :

Guideline/method :

Species :

Exposure period :

at °C

Concentration :

BCF :

Elimination :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark :

Reliability :

Reference :

## 4. Ecotoxicity

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### 4.1 ACUTE TOXICITY TO FISH

Type	: Acute toxicity to fish. Static exposure.
Guideline/method	:
Species	: <i>Lepomis macrochirus</i> (bluegill sunfish, freshwater)
Exposure period	: 96 hours
NOEC	:
LC0	:
LC50	: LC50 greater than tested concentration (100% of a 12% cobalt octoate solution).
LC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	: None reported
Year	: 1981
GLP	: Not reported
Test substance	: Cobalt octoate (12%), Lot No. 28702, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Light yellow liquid, mineral spirits odor. Purity and solubility not reported.
Method	: United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	: Test concentrations were control and 100% concentration of a 12% cobalt octoate solution. Test conducted in reconstituted freshwater (hardness = soft water) and temperature range of 20 – 21°C. Fish were < 1 year old and of same age class. Biological loading was 0.8 g/L
Result	: No mortality observed in 100% concentration of a 12% calcium octoate solution.
Remark	: <b>Supporting data for dissociation products:</b> <b>Acid:</b> The 96-h LC50 for fathead minnows ( <i>Pimephales promelas</i> ) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (Appendix B). <b>Metal:</b> For cobalt chloride, the 96-h LC50 was 1.41 mg Co/L for the highly sensitive rainbow trout, <i>Onchorynchus mykiss</i> . Other fish species are less sensitive with 96-h LC50 values ranging from 22.0 to 333 mg Co/L (Appendix G).
Reliability	: [3] Not reliable. Test material inadequately described. Lack of detail on methods. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. No analytical verification of test concentrations. Secondary reference, which contains apparent typographical error in description of test concentrations.
Reference	: Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.
Type	: Acute toxicity to fish. Static exposure.
Guideline/method	:
Species	: <i>Cyprinodon variegatus</i> (sheepshead minnow, saltwater)
Exposure period	: 96 hours
NOEC	:
LC0	:
LC50	: LC50 greater than tested concentration (100% of a 12% cobalt octoate solution).
LC100	:
Other	:
Other	:

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**Other** :  
**Limit test** :  
**Analytical monitoring** : None reported  
**Year** : 1981  
**GLP** : Not reported  
**Test substance** : Cobalt octoate (12%), Lot No. 28702, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Light yellow liquid, mineral spirits odor. Purity and solubility not reported.  
**Method** : United States Testing Company protocol PRO/FT, Fish, 365-0  
**Method detail** : Test concentrations were control and 100% concentration of a 12% cobalt octoate solution. Test conducted using synthetic seawater (28 ppt), temperature range of 19 - 22°C, fish < 1 yr old and of same age class, biological loading 0.9 g/L.  
**Result** : No mortality observed in 100% concentration of a 24% calcium octoate solution, for either species.  
**Remark** :  
**Reliability** : [3] Not reliable. Test material inadequately described. Lack of detail on methods. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. No analytical verification of test concentrations. Secondary reference.  
**Reference** : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

### 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

**Type** : Acute toxicity to daphnids. Static exposure.  
**Guideline/method** :  
**Species** : *Daphnia magna*  
**Exposure period** : 48 hours  
**NOEC** :  
**EC0** :  
**EC50** : 48-h EC50: 23% (95% CI: 15.3 – 34.5%)  
**EC100** :  
**Other** : 24-h EC50 could not be estimated because of insufficient mortality. 24-h EC50 > 32%  
**Other** :  
**Other** :  
**Limit test** :  
**Analytical monitoring** : None reported  
**Year** : 1981  
**GLP** : Not reported  
**Test substance** : Cobalt octoate (12%), Lot No. MCI #51-117099, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Blue-violet liquid, reported as insoluble in water. Purity not reported.  
**Method** : United States Testing Company protocol PRO/FT, Daphnia, 365-0  
**Method detail** : Test conducted in filtered (0.22 µ) lake water (hardness = soft), temperature range 20 - 21°C. Test concentrations were 0, 3.2, 10, 18 and 32% of cobalt octoate (12% solution). No information on test organisms.  
**Result** : 48-h EC50: 23% (95% CI: 15.3 – 34.5%); 24-h EC50: could not be calculated because of low mortality  
**Remark** : **Supporting data for dissociation products:**  
**Acid:** The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (Appendix B).  
**Metal:** For cobalt chloride, reported 48-h EC50 values for *Daphnia magna*

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- Reliability** : have been reported as 1.52 mg Co/L and as 5.5 mg Co/L. For *Ceriodaphnia dubia*, 48-h LC50 values ranged from 2.35 to 4.60 mg Co/L (Appendix G).  
: [3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished and no analytical verification of test concentrations. Lack of detail on methods. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Secondary reference.
- Reference** : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

### 4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

- Type** : Algal acute toxicity test
- Guideline/method** :
- Species** : *Selenastrum capricornutum* (freshwater green alga)
- Endpoint** : "growth" (not specified further; could be growth rate, yield or viability)
- Exposure period** : 96 hours
- NOEC** :
- LOEC** :
- EC0** :
- EC10** :
- EC50** : 0.03%
- Other** :
- Other** :
- Other** :
- Limit test** :
- Analytical monitoring** : None reported
- Year** : 1981
- GLP** : Not reported
- Test substance** : Cobalt octoate (12%), Lot No. MCI #51-117099, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Blue-violet liquid, reported as insoluble in water. Purity not reported.
- Method** : United States Testing Company protocol PRO/FT, Algae, 357-0
- Method detail** : Test concentrations were 0, 0.02, 0.03, 0.06, 0.10 and 0.18%. Stock solution prepared by adding an excessive amount of cobalt octoate (12%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used freshwater algal maintenance medium and test temperature 21 - 22°C.
- Result** : 96-h EC50 for was 0.03%. Confidence limits not reported.
- Remark** : **Supporting data for dissociation products:**  
**Acid:** For the green alga *Scenedesmus subspicatus*, the 96-h E<sub>50</sub>C50 (EC50 based upon biomass) was reported to be 40.616 mg/L and the 96-h E<sub>50</sub>C50 (EC50 based upon growth rate) was reported to be 44.390 mg/L for 2-ethylhexanoic acid (Appendix B).  
**Metal:** For cobalt chloride, the 96-h EC50 for *Chlorella vulgaris* was 0.52 mg/L. For the duckweed *Lemna minor*, the 7-d IC50 was 16.9 mg Co/L, while for the blue-green alga *Spirulina platensis* the 96-h EC50 was 23.8 mg Co/L (Appendix G).
- Reliability** : [3] Not reliable. Test material inadequately described and reported to be not soluble in water. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Test

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	concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard test conditions, lack of detail on methods. Secondary reference.
Reference	: Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.
Type	: Algal acute toxicity test
Guideline/method	:
Species	: <i>Skeletonema costatum</i> (saltwater diatom)
Endpoint	: "growth" (not specified further; could be growth rate, yield or viability)
Exposure period	: 96 hours
NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	: 15.0%
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	: None reported
Year	: 1981
GLP	: Not reported
Test substance	: Cobalt octoate (12%), Lot No. MCI #51-117099, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Blue-violet liquid, reported as insoluble in water. Purity not reported.
Method	: United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail	: Test concentrations were 0, 0.02, 0.03, 0.06, 0.10 and 0.18%. Stock solution prepared by adding an excessive amount of cobalt octoate (12%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used seawater algal medium I and test temperature 19 - 20°C
Result	: 96-h EC50 was 15.0%. Confidence limits not reported.
Remark	:
Reliability	: [3] Not reliable. Test material inadequately described and reported to be not soluble in water. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard test conditions, lack of detail on methods. Reported EC50 extrapolated well beyond range of test concentrations. Secondary reference.
Reference	: Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

### 4.4 ACUTE TOXICITY TO AVIAN SPECIES

Type	: Acute oral toxicity
Guideline/method	:
Species	: Bobwhite quail ( <i>Colinus virginianus</i> )

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<b>Number, sex and age of animals</b>	:	35 birds (16 males and 19 females), approximately 16 weeks old (200 ± 40 g)
<b>Exposure period</b>	:	14 days
<b>NOEL</b>	:	
<b>LD50</b>	:	Not stated, but less than half the birds died at the highest dose, therefore the LD50 would be > 2000 mg/kg.
<b>Other</b>	:	
<b>Other</b>	:	
<b>Other</b>	:	
<b>Limit test</b>	:	
<b>Analytical monitoring</b>	:	None reported
<b>Year</b>	:	1981
<b>GLP</b>	:	No
<b>Test substance</b>	:	Cobalt octoate, in corn oil vehicle
<b>Method</b>	:	
<b>Method detail</b>	:	Birds were housed in metal cages with wire floors, under a photoperiod of 17 hours light and 7 hours dark, mean humidity of 66% and mean temperature of 20°C (range 13 - 28°C). Birds were provided with water and standard diet ad libitum (except overnight starvation prior to dosing). Dose levels included vehicle control, 1000 mg/kg and 2000 mg/kg, administered by oral gavage. Mortalities were recorded daily. Body weights were recorded prior to dosing and at days 3, 7 and 14. Food consumption was recorded weekly. All birds were examined at death or test termination for gross pathology.
<b>Result</b>	:	Birds dosed at 1000 mg/kg showed no toxic effects immediately after dosing, but one bird was dead within 24 hours and surviving birds had become quiet. No further ill effects were observed in any birds after day 2 of the study. Birds dosed at 2000 mg/kg were quiet after dosing, but surviving birds appeared normal within 19 hours after dosing. In this group, 4 birds died over the course of the study. In exposed birds, large bodyweight decreases were observed during days 0 to 3 following dosing and continued at the higher dose for days 3 to 7. However both exposed groups showed an increase in food consumption over days 7 to 14, with concurrent mean bodyweight increases.
<b>Remark</b>	:	
<b>Reliability</b>	:	[3] Not reliable. Test material inadequately described. Secondary reference, with mortalities by day not presented.
<b>Reference</b>	:	Previously abstracted information from studies conducted by Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. Original study report not available.

## 5. Toxicity

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### 5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo :  
Type :  
Guideline/method :  
Species :  
Number of animals :  
    Males :  
    Females :  
Doses :  
    Males :  
    Females :  
Vehicle :  
Route of administration :  
Exposure time :  
Product type guidance :  
Decision on results on :  
    acute tox. tests :  
Adverse effects on :  
    prolonged exposure :  
Half-lives :  
    1<sup>st</sup>. :  
    2<sup>nd</sup>. :  
    3<sup>rd</sup>. :  
Toxic behavior :  
Deg. product :  
Deg. products CAS# :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

#### Supporting data for dissociation products:

**Acid:** Radiolabeled 2-ethylhexanoic acid was administered to female rats as follows: a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of  $0.19 \pm 0.11$  hrs,  $6.6 \pm 3.9$  hrs, and  $117 \pm 47$  hrs.

After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration ( $0.32 \pm 0.04$  hrs,  $6.8 \pm 3.5$  hrs, and  $98.2 \pm 32.8$  hrs). Dermal application resulted in slower absorption with peak blood levels occurring  $5.7 \pm 0.4$  hours after application and a half-life of  $3.2 \pm 0.1$  hr. Elimination was biphasic with half-lives of  $4.2 \pm 0.2$  and  $251 \pm 135$  hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

<u>Route</u>	<u>Dose</u>	<u>Percentage Excreted as</u>
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid; 2% unmetabolized 2-Ethylhexanoic acid
Oral (single)	100 mg/kg	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid; 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid; 2% unmetabolized 2-Ethylhexanoic acid

(Appendix B).

**Metal:** Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal, with increasing solubility resulting in increasing absorption. Approximately 13-34% of cobalt chloride, a soluble form, is absorbed in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine. Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (Appendix G).

Reliability :

## 5. Toxicity

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Reference :

### 5.1.1 ACUTE ORAL TOXICITY

**Type** : Acute Oral (LD50) Toxicity  
**Guideline/Method** :  
**Species** : Rat  
**Strain** : Sherman-Wistar albino  
**Sex** : Male and female  
**Number of animals** : Nine groups of 10 (5 male, 5 female)  
**Vehicle** :  
**Doses** : 0.63, 0.79, 1.00, 1.26, 1.58, 2.00, 2.51, 3.16, 3.98 g/kg  
**LD50** : For males: 1.55 g/kg (95% CI: 1.26 – 1.86 g/kg)  
For females: 1.22 g/kg (95% CI: 1.03 – 1.48 g/kg)  
**Year** : 1980  
**GLP** : Not reported  
**Test substance** : Cobalt octoate, 12%, (MC1 #51-11709), supplied by sponsor. Density approximately 1.02 g/mL.  
**Method** : Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.  
**Method detail** : Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation. Observed for 14-days post-exposure.  
**Result** : No symptoms were observed at the lowest dose. At intermediate doses, several animals died but surviving animals appeared to recover fully. All of the animals dosed at the three highest levels were dead within 24 hours. At doses of 2.51 g/kg and higher, animals were severely depressed, ataxic, ruffled, and drooling within 30 minutes of dosing; after 45-60 minutes they were comatose and most deaths occurred within 2-5 hours. Gross necropsies were unremarkable.  
**Remark** : **Supporting data for dissociation products:**  
**Acid:** The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (Appendix B). **Metal:** For cobalt chloride hexahydrate, the oral LD50 in rats was 766 mg/kg (equivalent to 190 mg Co/kg). Other reported LD50s range from 19.8 to 85.5 mg Co/mg bw in rats. In mice, the LC50 for cobalt chloride was reported as 89.3 mg Co/kg bw were reported (Appendix G).  
**Reliability** : [2] Reliable with restrictions. Basic data provided, exposure conditions not fully described, test material not described. Comparable to guideline.  
**Reference** : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

### 5.1.2 ACUTE INHALATION TOXICITY

**Type** : Limit Test  
**Guideline/method** :  
**Species** : Rat  
**Strain** : Albino  
**Sex** : Male and female  
**Number of animals** : 10 rats (5 male and 5 female in each group)  
**Vehicle** :  
**Doses** : One concentration, 10.0 mg/L of a 50% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.  
**Exposure time** : 1 hour  
**LC50** : > 10.0 mg/L (maximum attainable nominal concentration)

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Year	: 1980
GLP	: Not reported
Test substance	: Cobalt octoate 12% (MC1 #51-11709), prepared and used as a 50% w/v suspension in mineral spirits.
Method	:
Method detail	: Animals (200 – 205 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 72°F. Test material concentration was measured and determined to be 10.0 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 0.82 microns MMD (mass median diameter). Animals observed for 14 days post-exposure
Result	: No adverse effects were observed during the exposure period or during the two-week post exposure period. No mortality, no toxicity, and no adverse gross necropsy findings
Remark	: <b>Supporting data for dissociation products:</b> <b>Acid:</b> The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix B). <b>Metal:</b> No acute inhalation toxicity studies were located for cobaltous chloride (Appendix G).
Reliability	: [2] Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.
Reference	: Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

### 5.1.3 ACUTE DERMAL TOXICITY

Type	: Limit Test
Guideline/method	:
Species	: Rabbit
Strain	: Albino
Sex	: Male and female
Number of animals	: Six (3 male and 3 female)
Vehicle	:
Doses	: One dose, 5 g/kg
LD50	: > 5 g/kg
Year	: 1980
GLP	: Not reported
Test substance	: Cobalt octoate, 12%, MC1 #51-11709, supplied by sponsor. Density approx. 1.02 g/mL.
Method	: Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail	: Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious dressing. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure. Gross autopsies conducted on all dead and surviving animals.
Result	: No mortality. Substantial skin irritation lasting several days was observed. No adverse gross necropsy findings in this limit test.
Remark	: <b>Supporting data for dissociation products:</b> <b>Acid:</b> The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted)

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was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg. (Appendix B).

**Metal:** Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (Appendix G).

**Reliability** : [2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.

**Reference** : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

### 5.2.1 SKIN IRRITATION

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :  
Concentration :  
Exposure :  
Exposure time :  
Number of animals :  
Vehicle :  
Classification :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

**Supporting data for dissociation products:**

**Acid:** 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (Appendix B).

**Metal:** Dermatitis is a common result of dermal exposure to cobalt in humans and is probably caused by an allergic reaction (Appendix G).

Reliability :  
Reference :

### 5.2.2 EYE IRRITATION

Type :  
Guideline/method :  
Species :  
Strain :  
Sex :  
Concentration :  
Dose :  
Exposure time :  
Number of animals :  
Vehicle :  
Classification :  
Year :  
GLP :  
Test substance :

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Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours. No observations were made beyond 24 hours to assess recovery. (Appendix B).
Reliability	:	
Reference	:	

### 5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	<b>Supporting data for dissociation products:</b> <b>Acid:</b> Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery.  Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflect lower terminal body weight. Hepatocyte

hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Study H, Appendix B). These data are consistent with four previous repeated dose studies in Fischer rats (Appendix B). In a similar 13-week dietary exposure study with B6C3F1 mice, the NOAEL was approximately 200 mg/kg-day (Study G, Appendix B).

**Metal:** Repeated oral dosing of rats with cobalt chloride hexahydrate for 8 weeks indicated the NOAEL was 0.6 mg Co/kg and the LOAEL was 2.5 mg Co/kg, based upon changes in hemoglobin content and numbers of erythrocytes. Another study reported oral doses of 0.5 and 2.5 mg Co/kg for 7 months stimulated hematopoiesis and decreased immunological reactivity in rats, while doses of 0.05 mg Co/kg had no effects. (Appendix G).

Reliability :  
Reference :

#### 5.5 GENETIC TOXICITY 'IN VITRO'

Type	: Mutagenicity
Guideline/method	:
System of testing	: Ames assay, standard plate assay
Species	: <i>Salmonella typhimurium</i>
Strain	: TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	: 5, 10, 50, 100, and 500 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:
Metabolic activation	: Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254, as per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year	: 1980
GLP	: No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	: Cobalt octoate 12% (12.1), MCI No. 51-11709; dark purple liquid
Method	: Followed method of Ames et. al.
Method detail	: 0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37°C and number of colonies compared to background. No further details provided.
Result	: Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of <i>S. typhimurium</i> tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response. Precipitate formed at highest dose level.
Remark	: <b>Supporting data for dissociation products:</b> <b>Acid:</b> In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid, either with or without activation (See Appendix B). <b>Metal:</b> Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt chloride, are generally non-mutagenic in bacterial assays, including plate incorporation and fluctuation assays with <i>Salmonella typhimurium</i> TA strains and <i>Escherichia coli</i> WP2. However, a weak positive mutagenic response has been found in the rec assay with <i>Bacillus subtilis</i> and in Chinese hamster V9 cells. DNA damage in isolated

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	human lymphocytes was observed at 6.0 mg Co/L in the alkaline comet assay, and an increase in sister chromatid exchanges has been observed in human lymphocytes and macrophages (Appendix G).
Reliability	: [2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	: Van Goethem, D., 1980. Evaluation of cobalt octoate in the <i>Salmonella</i> /Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).
Type	: Mutagenicity
Guideline/method	:
System of testing	: Bacterial DNA damage or repair assay
Species	: <i>Escherichia coli</i>
Strain	: W3110 (pol A <sup>+</sup> ) and its DNA polymerase deficient derivative p3478 (pol A <sup>-</sup> )
Test concentrations	: 5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:
Metabolic activation	: With and without. Activation with S-9 from Aroclor 1254 induced rat liver as per Ames al., 1975, Mut. Res. 31:347-364
Year	: 1981
GLP	: No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	: Cobalt octoate 12% (12.1), MCI No. 51-11709; dark purple liquid
Method	: Followed method of Rosenkranz et al. (1971).
Method detail	: Test material (5 concentrations) applied to cells in culture. Vehicle controls (ethanol) and negative controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10 <sup>4</sup> ) of each strain were exposed to the test material for 1 hour at 37°C. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37°C and the number of viable cells determined.
Result	: Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A <sup>+</sup> to pol A <sup>+</sup> survivors), with or without activation. Survival index at all dose levels was greater than 0.80. A precipitate formed at the highest dose level which confounds the interpretation of results at this level.
Remark	:
Reliability	: [2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	: Van Goethem, D., 1981. Evaluation of cobalt in the <i>E.coli</i> DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

### 5.6 GENETIC TOXICITY 'IN VIVO'

Type	: Micronucleus mutagenicity assay
Guideline/method	:
Species	: Mouse
Strain	: Specific Pathogen Free mice of the COBS CD-1 (ICR) BR (ICR derived) strain
Sex	: Male and female
Number of animals	: 5 males and 5 females per dose level (including vehicle control and positive control)
Route of admin.	: Oral gavage, using corn oil vehicle
Exposure period	: Thirty hours (dosing at 0 and 24 hours, followed by 6 hours observation)

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<b>Doses</b>	: 625, 1250 and 2500 mg/kg, given twice (24 hours apart) to produce total dose levels of 1250, 2500 and 5000 mg/kg. Corn oil control (0.1 mL/10g via gavage) and Mitomycin C positive control (injected i.p. at 4 mg/kg two times for a total dose of 8 mg/kg).
<b>Year</b>	: 1981
<b>GLP</b>	: Yes
<b>Test substance</b>	: Cobalt octoate (12%), [Cobalt 2-ethylhexanoate (12%)], batch #MCI 51-11709; clear dark purple liquid, specific gravity 1.01.
<b>Method</b>	:
<b>Method detail</b>	: Preliminary toxicity study was used to select upper dose for micronucleus test. Animals (18 – 21 g) fasted overnight and orally dosed (two doses, 24 hours apart). Standard volume per dose was 0.1 mL/10 g body weight. At the lowest dose, temporary lethargy was observed. Toxic symptoms (pilo-erection and lethargy at 2500 mg/kg and these symptoms plus hypopnea at 5000 mg/kg) were observed one-half hour after dosing but were not evident several hours later. Two deaths occurred at the highest dose. At the end of 30 hours, all animals were sacrificed. Femurs were cleared and one epiphysis removed from each bone; a bone marrow smear was made onto a slide containing calf serum, cleaned in methanol for 24 hours, air dried, fixed in methanol overnight, air dried, placed in buffer distilled water and stained with Giemsa. The number of micronucleated cells per 1000 polychromatic erythrocytes per animal and the rate of normochromatic to polychromatic erythrocytes was determined. Comparisons to control were made using Wilcoxon's Sum of Ranks test at $p > 0.10$ .
<b>Result</b>	: No evidence of mutagenic potential was found. Test material groups produced micronucleated cell counts comparable to the vehicle control and to historical controls (0.1 – 1.8). Positive control response indicated a mean of 78.1 micronucleated cells per 1000 polychromatic erythrocytes. Ratio of normochromatic to polychromatic erythrocytes was comparable in test material and vehicle control groups (1.52). The positive control gave an increased ratio of 8.53.
<b>Remark</b>	: <b>Supporting data for dissociation products:</b> <b>Acid:</b> 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix B). <b>Metal:</b> Oral administration of cobalt chloride hexahydrate to mice (20 – 80 mg/kg bw) produced a concentration-dependent increase in chromosomal aberrations. A dose-dependent increase in the incidence of micronucleated polychromatic erythrocytes was observed in mice subsequent to i.p. injection of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ , at doses of 25 – 90 mg Co/kg bw. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL). (Appendix G).
<b>Reliability</b>	: [2] Reliable with restrictions. Comparable to guideline. Incomplete description of test material.
<b>Reference</b>	: Richold, M., and Richardson, J.C., 1981. Micronucleus test on Cobalt Octoate 12% [Cobalt 2-ethylhexanoate (12%)], study conducted for Tenneco Chemicals, Inc. by Huntingdon Research Centre, Huntingdon, England.

### 5.8.2 DEVELOPMENTAL TOXICITY

<b>Type</b>	:
<b>Guideline/method</b>	:
<b>Species</b>	:
<b>Strain</b>	:
<b>Sex</b>	:

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Route of admin. :  
Exposure period :  
Frequency of treatment :  
Duration of test :  
Doses :  
Control group :  
NOAEL maternal tox. :  
NOAEL teratogen. :  
Other :  
Other :  
Other :  
Year :  
GLP :  
Test substance :  
Method :  
Method detail :  
Result :  
Remark :

### **Supporting data for dissociation products:**

**Acid:** Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (Appendix B). In the most reliable study (Studies E and F, Appendix B), the NOEL for teratogenic and developmental effects in rats was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight were noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryotoxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters was significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternbrae occurred primarily in the high-dose group and

occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(Appendix B, Studies E & F).

**Metal:** In a developmental toxicity study with cobalt chloride exposure (5.4 to 21.8 mg Co/kg/day) in rats from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects were observed on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (Appendix G).

Reliability  
Reference

:  
:

## 5.8.3 TOXICITY TO REPRODUCTION

Type :  
 Guideline/method :  
 In vitro/in vivo :  
 Species :  
 Strain :  
 Sex :  
 Route of admin. :  
 Exposure period :  
 Frequency of treatment :  
 Duration of test :  
 Doses :  
 Control group :  
 Year :  
 GLP :  
 Test substance :  
 Method :  
 Method detail :  
 Result :  
 Remark :

**Supporting data for dissociation products:**

**Acid:** A One-Generation Reproduction Toxicity Study (OECD 415) was conducted with 2-ethylhexanoic acid (as sodium 2-ethylhexanoate). Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair

appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

This study did not provide information on water consumption, concentration of test substance in drinking water, or incidence of effect within animal or litter. There was no analysis of dosing solutions. No criteria were provided to indicate how many abnormal sperm were required for a positive response. All animals were naïve and not proven breeders, so reduced mating success may not be treatment-related. No confirmation of estrous cycle; no data on effect of the test substance on gestation period. Thus, the apparent effect on physical development of pups from the high-dose group may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals within a group to be a reliable indicator of male function. (Appendix B).

**Metal:** Cobalt exposure (as cobalt chloride hexahydrate in drinking water for 12 -13 weeks) affected male reproductive parameters for mice in a time- and dose-dependent manner. All dose levels (23.0 – 72.1 mg Co/kg-day) caused decreases in testicular weight and epididymal sperm concentration. Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (Appendix G).

Reliability :  
Reference :

## 6.0 OTHER INFORMATION

### 6.1 CARCINOGENICITY

**Metal:** The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals. "No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt." (ATSDR Sept 2001 Draft; see Appendix G).